

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



B7

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>C07K 14/00</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 98/25959</b> <b>(43) International Publication Date:</b> 18 June 1998 (18.06.98)
<b>(21) International Application Number:</b> PCT/US97/22787 <b>(22) International Filing Date:</b> 11 December 1997 (11.12.97) <b>(30) Priority Data:</b> 60/032,757 11 December 1996 (11.12.96) US <b>(71) Applicant:</b> CHIRON CORPORATION (US/US); 4560 Horton Street, Emeryville, CA 94608 (US). <b>(72) Inventors:</b> ESCOBEDO, Jaime; 1470 Livorna Road, Alamo, CA 94507 (US). HU, Quianjin; Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608 (US). GARCIA, Pablo; 882 Chenery Street, San Francisco, CA 94131 (US). WILLIAMS, Lewis, T.; 3 Miraflores Lane, Tibouron, CA 94920 (US). KOTHAKOTA, Srinivas; Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608 (US). <b>(74) Agents:</b> POTTER, Jane, E., R.; Chiron Corporation, Intellectual Property - R440, P.O. Box 8097, Emeryville, CA 94662-8097 (US) et al.		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> SECRETED HUMAN PROTEINS  <b>(57) Abstract</b>  Secreted proteins can be identified using a method which exploits the ability of microsomes to modify proteins post-translationally. Nineteen human secreted proteins and full-length cDNA sequences encoding the proteins have been identified using this method. The proteins and cDNA sequences can be used, <i>inter alia</i> , for targeting other proteins to the membrane or extracellular milieu.		

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## SECRETED HUMAN PROTEINS

5 This application claims the benefit of copending provisional application  
Serial No. 60/032,757, filed December 11, 1996, which is incorporated herein by  
reference.

### TECHNICAL AREA OF THE INVENTION

10 The invention relates to the area of proteins. More particularly, the  
invention relates to human secreted proteins.

### BACKGROUND OF THE INVENTION

15 Secreted proteins include such important proteins as growth factors,  
cytokines and their receptors, extracellular matrix proteins, and proteases.  
Nucleotide sequences encoding these proteins can be used to detect disease states in  
which such proteins are implicated and to develop therapeutics for such diseases.  
Thus, there is a need in the art for methods of identifying secreted proteins and the  
nucleotide sequences which encode them.

### SUMMARY OF THE INVENTION

20 It is an object of the invention to provide an isolated and purified human  
protein.

It is yet another object of the invention to provide a fusion protein.

It is still another object of the invention to provide a preparation of antibodies.

It is even another object of the invention to provide an isolated and purified subgenomic polynucleotide.

5 It is yet another object of the invention to provide an isolated gene.

It is a further object of the invention to provide a DNA construct for expressing all or a portion of a human protein.

It is still another object of the invention to provide a host cell comprising a DNA construct.

10 It is another object of the invention to provide a homologously recombinant cell.

It is even another object of the invention to provide a method of producing a human protein.

15 It is another object of the invention to provide a method of identifying a secreted polypeptide which is modified by rough microsomes.

These and other objects of the invention are provided by one or more of the embodiments described below.

20 One embodiment of the invention provides an isolated and purified human protein. The isolated and purified human protein has an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

25 Another embodiment of the invention provides an isolated and purified human protein having an amino acid sequence which is at least 85% identical to an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

30 Still another embodiment of the invention provides a polypeptide comprising at least 6 contiguous amino acids of an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

Even another embodiment of the invention provides a fusion protein. The fusion protein comprises a first protein segment and a second protein segment fused together by means of a peptide bond. The first protein segment consists of at least 6 contiguous amino acids selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

Yet another embodiment of the invention provides a preparation of antibodies. The antibodies specifically bind to a human protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

Even another embodiment of the invention provides an isolated and purified subgenomic polynucleotide. The isolated and purified subgenomic polynucleotide has a nucleotide sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19.

Yet another embodiment of the invention provides an isolated and purified subgenomic polynucleotide consisting of at least 10 contiguous nucleotides selected from the group consisting of the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19.

Still another embodiment of the invention provides an isolated gene. The isolated gene corresponds to a cDNA sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19.

Another embodiment of the invention provides a DNA construct for expressing all or a portion of a human protein. The DNA construct comprises a promoter and a polynucleotide segment. The polynucleotide segment encodes at least 6 contiguous amino acids of a human protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

The polynucleotide segment is located downstream from the promoter.

Transcription of the polynucleotide segment initiates at the promoter.

Even another embodiment of the invention provides a host cell comprising a DNA construct. The DNA construct comprises a promoter and a polynucleotide segment. The polynucleotide segment encodes at least 6 contiguous amino acids of a human protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38. The polynucleotide segment is located downstream from the promoter. Transcription of the polynucleotide segment initiates at the promoter.

Still another embodiment of the invention provides a homologously recombinant cell having incorporated therein a new transcription initiation unit. The transcription initiation unit comprises in 5' to 3' order an exogenous regulatory sequence, an exogenous exon, and a splice donor site. The transcription initiation unit is located upstream to a coding sequence of a gene. The gene comprises a nucleotide sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19. The exogenous regulatory sequence controls transcription of the coding sequence of the gene.

Yet another embodiment of the invention provides a method of producing a human protein. A culture of a cell is grown. The cell comprises a DNA construct. The DNA construct comprises a promoter and a polynucleotide segment. The polynucleotide segment encodes at least 6 contiguous amino acids of a human protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38. The polynucleotide segment is located downstream from the promoter. Transcription of the polynucleotide segment initiates at the promoter. The protein is purified from the culture.

Even another embodiment of the invention provides a method of producing a human protein. A culture of a cell is grown. The cell comprises a new transcription initiation unit. The transcription initiation unit comprises in 5' to 3'

order an exogenous regulatory sequence, an exogenous exon, and a splice donor site. The transcription initiation unit is located upstream to a coding sequence of a gene. The gene comprises a nucleotide sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,  
5 12, 13, 14, 15, 16, 17, 18, and 19. The exogenous regulatory sequence controls transcription of the coding sequence of the gene. The protein is purified from the culture.

Another embodiment of the invention provides a method of identifying a secreted polypeptide which is modified by rough microsomes. A population of  
10 cDNA molecules is transcribed *in vitro* whereby a population of cRNA molecules is formed. A first portion of the population of cRNA molecules is translated *in vitro* in the absence of rough microsomes whereby a first population of polypeptides is formed. A second portion of the population of cRNA molecules is translated *in vitro* in the presence of rough microsomes whereby a second population of  
15 polypeptides is formed. The first population of polypeptides is compared with the second population of polypeptides. Polypeptide members of the second population which have been modified by the rough microsomes are detected.

The present invention thus provides the art with a method for identifying secreted proteins or polypeptides, the amino acid sequences of nineteen novel  
20 human secreted proteins, and the nucleotide sequences which encode these proteins. The invention can be used to, *inter alia*, to produce secreted proteins for therapeutic and diagnostic purposes.

#### **DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

25 The inventors have discovered a method for identifying secreted proteins or polypeptides. Secreted proteins or polypeptides include soluble proteins which can be transported across a membrane, such as a cell membrane, nuclear membrane, or membrane of the endoplasmic reticulum, as well as proteins which can be partially secreted from a cell, such as membrane-bound receptors.

30 Secreted proteins can contain a signal (or secretion leader) sequence, located at the N-terminus and including at least several hydrophobic amino acids,

such as phenylalanine, methionine, leucine, valine, or tryptophan. Non-hydrophobic amino acids can also be included in the signal sequence. Signal sequences are described in von Heijne, *J. Mol. Biol.* 184:99-105 (1985) and Kaiser and Botstein, *Mol. Cell. Biol.* 6:2382-2391 (1986). Secreted proteins can also be glycosylated by post-translational modification. The presence of a signal sequence or the presence of glycosylation or both indicate that a particular protein is a secreted protein.

In order to identify secreted proteins or polypeptides, the method of the invention exploits properties of microsomes, which are the closed vesicles that result from fragmentation of endoplasmic reticulum. Microsomes can be rough or smooth, depending on whether the endoplasmic reticulum from which they were derived is studded with ribosomes. Microsomes, particularly rough microsomes, have the ability to perform post-translational modifications, such as glycosylation and cleavage of signal sequences from proteins or polypeptides.

To identify secreted proteins, a population of complementary DNA (cDNA) molecules is transcribed *in vitro* to synthesize a population of complementary RNA (cRNA) molecules. The cDNA molecules can be synthesized by reverse transcription of mRNA molecules isolated from a particular cell or tissue type or organism using, for example, a commercially available reverse transcriptase enzyme. Alternatively, the reverse transcription reaction to form cDNA molecules can be conducted on total RNA, without a preliminary purification of mRNA.

Any organism, such as a bacterium, plant, invertebrate, or vertebrate organism, can be used as a source of RNA. Particularly preferred sources of RNA are mammals, most preferably humans. Tissues, such as liver, brain, kidney, spleen, pancreas, or muscle, can be used as a source of RNA. Individual cell types, either primary cells or members of established cell lines, such as HeLa, CHO, PC12, P19, BHK, COS, or HepG2, are suitable sources of RNA. Tissues or primary cells isolated from organisms at a particular stage in development can be used as RNA sources. Stem cells, such as hematopoietic, neuronal, and embryonic stem cells, can also be used as a source of RNA.

Total RNA or mRNA can be isolated using methods known in the art. Such methods are described, *inter alia*, in Sambrook *et al.*, MOLECULAR CLONING, A



LABORATORY MANUAL (2d ed., Cold Spring Harbor Press, N.Y., 1989), and Ausubel *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (Greene Publishing Associates and John Wiley & Sons, N.Y., 1994). Techniques for RNA isolation can be tailored for a particular organism or cell type, as is known in the art.

5 Complementary DNA can optionally be obtained from a cDNA library. The cDNA library can be derived from the genome of any organism of interest, particularly a mammal or a human. Tissue- or cell type-specific cDNA libraries can also be used as a source of cDNA.

10 Transcription of cDNA molecules *in vitro* to form cRNA molecules can be carried out using any methods known in the art. These methods include, for example, placing cDNA into a cloning vector containing a promoter, such as an SP6, T7, or T3 polymerase promoter, and transcribing the cDNA using the appropriate polymerase. A variety of commercial kits are available for this purpose.

15 A first portion of the population of cRNA molecules can be translated *in vitro*, in the absence of rough microsomes, to form a first population of polypeptides which have not been post-translationally modified. A second portion of the population of cRNA molecules can be translated *in vitro* in the presence of rough microsomes. Under the conditions of the *in vitro* translation reaction, rough microsomes can cleave signal sequences from those polypeptides which comprise  
20 such sequences. Under the same conditions, rough microsomes can also glycosylate those polypeptides which contain glycosylation sites.

25 Methods of *in vitro* translation are those which are known in the art, such as translation in a reticulocyte lysate system, particularly a rabbit reticulocyte lysate. Reticulocyte lysate systems can be assembled in the laboratory or purchased commercially in kit form.

30 Microsomes can be prepared by disruption of tissues or cells by homogenization, as is known in the art. If desired, rough and smooth microsomes can be separated using well-known techniques, such as sucrose density gradient sedimentation. Microsomes are also available commercially, for example, such as the canine pancreatic microsomes available from Promega Corp., Madison, WI.

The first population of polypeptides can then be compared with the second population of polypeptides. This comparison can be by means of, for example, one- or two-dimensional polyacrylamide gel electrophoresis, as is known in the art. Polypeptides separated in the gels can be detected by any means known in the art, such as staining with copper, silver, Coomassie Brilliant Blue, amido black, fast green FCF, Ponceau S, or a chromophoric label. Separated proteins can also be visualized using radioactive, chemiluminescent, fluorescent, or enzymatic tags incorporated into the proteins before separation.

The gels can be dried or the proteins can be transferred to membranes, such as polyvinylidene difluoride membranes. Either the gels or membranes themselves or photographs of the gels or membranes can be compared by eye. Alternatively, the gels or membranes can be scanned, for example, with a densitometer and analyzed with the aid of a computer.

Polypeptide members of the second population of polypeptides, which have been modified by the rough microsomes, can be detected by any means available in the art. For example, a shift in the position of a polypeptide band can be observed, indicating an increase in molecular weight of a member of the second population compared with the corresponding polypeptide member of the first population. Such an increase in molecular weight indicates that the polypeptide member of the second population was glycosylated by the rough microsomes.

A shift in the position of a polypeptide band indicating a decrease in molecular weight of a member of the second population compared with the corresponding polypeptide member of the first population can also be observed. This decrease in molecular weight indicates that the polypeptide member of the second population contained a signal sequence which was cleaved by the rough microsomes.

Polypeptides which are modified by the rough microsomes are identified as secreted polypeptides. Optionally, quantities of cDNA molecules which encode secreted polypeptides can be obtained. Molecules of cDNA which encode polypeptides which are post-translationally modified by the rough microsomes can be placed into suitable vectors using standard recombinant DNA techniques and

used to transform host cells. Many vectors are available for this purpose, such as retroviral or adenoviral vectors and bacteriophage, as described below.

Vectors comprising cDNA which encode secreted polypeptides can be introduced into host cells using techniques available in the art. These techniques include, but are not limited to, transferrin-polycation-mediated DNA transfer, transfection with naked or encapsulated nucleic acids, liposome-mediated cellular fusion, intracellular transportation of DNA-coated latex beads, protoplast fusion, viral infection, electroporation, and calcium phosphate-mediated transfection.

The host cells can be any host cells which are capable of propagating cDNA molecules. A variety of host cells, for example immortalized cell lines such as HeLa, CHO, or HEK, are available for this purpose.

Transformed host cells can be diluted serially and cultured to form individual colonies. Methods of culturing host cells and the media suitable for each host cell type are well known in the art. Preferably, each colony originates from a single transformed host cell. Separate preparations of cDNA from each colony can be prepared, as described above, and transcribed *in vitro* to form cRNA. The cRNA can be transcribed to form secreted polypeptides, which can be purified as is known in the art. If the preparation of secreted polypeptides from a colony contains more than one species of polypeptide, the steps described above can be repeated until a colony is obtained which contains cDNA encoding only a single species of polypeptide.

Complementary DNA molecules which encode secreted proteins can be sequenced using standard nucleotide sequencing techniques. The sequence of each cDNA molecule can be compared with known sequences in a database to determine whether the clone encodes a known or a novel secreted protein.

The inventors have used the method of the invention to identify nineteen novel human secreted proteins. Amino acid sequences for these nineteen human secreted proteins are disclosed in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38. Nucleotide sequences which encode the proteins are disclosed in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19, respectively.

Clones containing the cDNAs of the secreted proteins were deposited on December 11, 1997, with the ATCC. Individual bacterial cells (*E. coli*) in this composite deposit contain one or more of the polynucleotides encoding the secreted proteins of the invention and can be retrieved using an oligonucleotide probe designed from the sequence for that particular polynucleotide, as provided herein. Each polynucleotide can be removed from the vector by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI). The deposit submitted to the ATCC has been designated SECP120997. The nucleotide sequences of these deposits and the amino acid sequences they encode are controlling in the event of a discrepancy between the amino acid and nucleotide sequences disclosed herein and those contained in the deposits.

A purified and isolated subgenomic polynucleotide of the present invention comprises at least 10, 12, 15, 18, 20, 25, 30, 35, 40, 45, or 50 contiguous nucleotides selected from the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19. The isolated and purified subgenomic polynucleotides can comprise an entire nucleotide sequence selected from the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19.

Subgenomic polynucleotides contain less than a whole chromosome and are preferably intron-free. Polynucleotides of the invention can be isolated and purified free from other nucleotide sequences by standard nucleic acid purification techniques, using restriction enzymes and probes to isolate fragments comprising the coding sequences.

Isolated genes corresponding to the cDNA sequences disclosed herein are also provided. Known methods can be used to isolate the corresponding genes using the provided cDNA sequences. These methods include preparation of probes or primers from the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19 for use in identifying or amplifying the genes from human genomic libraries or other sources of human genomic DNA.

The coding sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19 can be made using reverse transcriptase with

human mRNA as a template. Amplification by PCR can also be used to obtain the polynucleotides, using either genomic DNA or cDNA as a template. Polynucleotide molecules of the invention can also be made using the techniques of synthetic chemistry given the sequences disclosed herein. The degeneracy of the genetic code permits alternate nucleotide sequences which will encode the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38 to be synthesized. All such nucleotide sequences are within the scope of the present invention.

Polynucleotide molecules of the invention can be propagated in vectors and cell lines as is known in the art. Polynucleotide molecules can be on linear or circular molecules. They can be on autonomously replicating molecules or on molecules without replication sequences. For propagation, polynucleotides of the invention can be introduced into suitable host cells using any techniques available in the art, as described above.

Subgenomic polynucleotides of the invention can be used to propagate additional copies of the polynucleotides or to express protein, polypeptides, or fusion proteins. The subgenomic polynucleotides disclosed herein can also be used, for example, as biomarkers for tissues or chromosomes, as molecular weight markers for DNA gels, to elicit immune responses, such as the formation of antibodies against single- or double-stranded DNA, and in DNA-ligand interaction assays, to detect proteins or other molecules which interact with the nucleotide sequences.

Disease states may be associated with alterations in the expression of genes which encode proteins of the invention. Polynucleotide sequences disclosed herein can also be used to determine the involvement of any of these sequences in disease states. For example, a gene in a diseased cell can be sequenced and compared with a wild-type coding sequence of the invention. Alternatively, nucleotide probes can be constructed and used to detect normal or altered (mutant) forms of mRNA in a diseased cell. Subgenomic polynucleotides of the invention can also be used to design diagnostic tests and therapeutic compositions for diseases which may be associated with altered expression of these genes.

The present invention provides both full-length and mature forms of the disclosed proteins. Full-length forms of the proteins have the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38. The full-length forms of a protein can be processed enzymatically to remove a signal sequence, resulting in a mature form of the protein. Signal sequences can be identified by examination of the amino acid sequences disclosed herein and comparison with amino acid sequences of known signal sequences (see, *e.g.*, von Heijne, 1985; Kaiser & Botstein, 1986). Similarly, transmembrane domains can be identified by examination of the amino acid sequences disclosed herein. A transmembrane domain typically contains a long stretch of 15-30 hydrophobic amino acids.

Other domains with predicted functions can also be identified. For example, the protein having the amino acid sequence shown in SEQ ID NO:23 comprises a Kunitz type serine protease inhibitor domain spanning amino acids 68 to 122 of SEQ ID NO:23. The protein having the amino acid sequence shown in SEQ ID NO:20 contains a zinc-finger motif.

Allelic variants of the disclosed subgenomic polynucleotides can occur and encode proteins which are identical, homologous, or substantially related to amino acid sequences disclosed herein (see below).

Allelic variants of subgenomic polynucleotides of the invention can be identified by hybridization of putative allelic variants with nucleotide sequences disclosed herein under stringent conditions. For example, by using the following wash conditions--2 x SCC, 0.1% SDS, room temperature twice, 30 minutes each; then 2 x SCC, 0.1% SDS, 50 °C. once, 30 minutes; then 2 x SCC, room temperature twice, 10 minutes each--allelic variants can be identified which contain at most about 25-30% basepair mismatches. More preferably, allelic variants contain 15-25% basepair mismatches, even more preferably 5-15% basepair mismatches.

Protein variants of secreted proteins of the invention are also included. Amino acids which are not involved in regions which determine biological activity can be deleted or modified without affecting biological function. Preferably, protein

variants of the invention have amino acid sequences which are at least 85%, 90%, or 95% identical to the amino acid sequences disclosed herein and have similar biological properties (see below). More preferably, the molecules are 98% identical. Modifications of interest in the protein sequences can include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue. Proteins or derivatives can be either glycosylated or unglycosylated. Techniques for making such modifications are well known to those skilled in the art (see, e.g., U.S. 4,518,584). Alternatively, variants of proteins disclosed herein can be constructed using techniques of synthetic chemistry or using recombinant DNA methods.

Preferably, amino acid changes in variants or derivatives of proteins of the invention are conservative amino acid changes, *i.e.*, substitutions of similarly charged or uncharged amino acids. A conservative amino acid change involves substitution of one amino acid for another amino acid of a family of amino acids which are structurally related in their side chains. Naturally occurring amino acids are generally divided into four families: acidic (aspartate, glutamate), basic (lysine, arginine, histidine), non-polar (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cystine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified as aromatic amino acids. It is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the binding properties of the resulting molecule, especially if the replacement does not involve an amino acid at a binding site involved in an interaction of the protein. Non-naturally occurring amino acids can also be used to form protein variants of the invention.

Whether an amino acid change results in a functional protein or polypeptide can readily be determined by assaying biological properties of the disclosed proteins or polypeptides, as described below. Species homologs of human subgenomic polynucleotides and proteins of the invention can also be identified by making

suitable probes or primers and screening cDNA expression libraries from other species, such as mice, monkeys, yeast, or bacteria.

In the case of proteins which are membrane-bound, such as cell surface receptor proteins, soluble forms of the proteins can be obtained by deleting the nucleotide sequences which encode part or all of the intracellular and transmembrane domains of the protein and expressing a fully secreted form of the protein in a host cell. Techniques for identifying intracellular and transmembrane domains, such as homology searches, can be used to identify such domains in proteins of the invention using amino acid and nucleotide sequences disclosed herein.

Polypeptides consisting of less than full-length proteins of the present invention are also provided. Polypeptides of the invention can be linear or can be cyclized, for example, as described in Saragovi *et al.*, 1992, *Bio/Technology* 10, 773-778 and McDowell *et al.*, 1992, *J. Amer. Chem. Soc.* 114, 9245-9253.

Polypeptides can be used, for example, as immunogens, diagnostic aids, or therapeutics, and to create fusion proteins, as described below.

Polypeptide molecules consisting of less than the entire amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38 are also provided. Such polypeptides comprise at least 6, 8, 10, 12, 15, 18, or 20 contiguous amino acids of an amino acid sequence shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38. Polypeptide molecules of the invention can also possess minor amino acid alterations which do not substantially affect the ability of the polypeptides to interact with specific molecules, such as antibodies.

Derivatives of the polypeptides, such as glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties, are also provided. Derivatives also include allelic variants, species variants, and muteins. Covalent derivatives are prepared by linkage of functionalities to groups which are found in the amino acid chain or at the N- or C-terminal residue by means known in the art. Truncations or deletions of regions which do not affect biological function are also encompassed. Truncated or deleted



polypeptides can be prepared synthetically or recombinantly, or by proteolytic digestion of purified or partially purified secreted proteins of the invention.

5 Fusion proteins comprising at least 6, 8, 10, 12, 15, 18, or 20 contiguous amino acids of the disclosed proteins can also be constructed. Human fusion proteins are useful, *inter alia*, for generating antibodies against amino acid sequences and for use in various assay systems. For example, fusion proteins can be used to identify proteins which interact with secreted proteins of the invention and influence their function. Physical methods, such as protein affinity chromatography, or library-based assays for protein-protein interactions, such as the  
10 yeast two-hybrid or phage display systems, can be used for this purpose. Such methods are well known in the art and can also be used as drug screens. Fusion proteins can also be used to target molecules to a specific location in a cell or to cause a molecule to be secreted or to be anchored in a cellular membrane.

15 Fusion proteins of the invention comprise two protein segments which are fused together with a peptide bond. The first protein segment comprises at least 6, 8, 10, 12, 15, 18, or 20 contiguous amino acids selected from an amino acid sequence shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38. The first protein segment can also be a full-length protein (comprising a signal sequence) or a mature protein (lacking a signal  
20 sequence). The second protein segment can be a full-length protein or a protein fragment. The second protein or protein fragment can be labeled with a detectable marker, such as a radioactive, chemiluminescent, biotinylated, or fluorescent tag, or can be an enzyme which will generate a detectable product. Enzymes suitable for this purpose, such as  $\beta$ -galactosidase, are well known in the art.

25 Techniques for making fusion proteins, either recombinantly or by covalently linking two protein segments, are well known in the art. Fusion proteins comprising amino acid sequences of the invention can also be constructed, for example, using standard recombinant DNA methods to make a DNA construct which comprises contiguous nucleotides selected from SEQ ID NOs:1, 2, 3, 4, 5, 6,  
30 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19 and encoding the desired amino

acids in proper reading frame with nucleotides encoding the second protein segment.

Proteins or polypeptides of the invention can be purified free from other components with which they are normally associated in a cell, such as carbohydrates, lipids, subcellular organelles, or other proteins. An isolated protein or polypeptide is at least 90% pure. Preferably, the preparations are 95% or 99% pure. The purity of a preparation can be assessed, for example, by examining electrophoretograms of protein or polypeptide preparations at several pH values and at several polyacrylamide concentrations, as is known in the art.

Standard biochemical methods can be used to isolate proteins of the invention from tissues which express the proteins or to isolate proteins, polypeptides, or fusion proteins from recombinant host cells into which a DNA construct has been introduced. Methods of protein purification, such as size exclusion chromatography, ammonium sulfate fractionation, ion exchange chromatography, affinity chromatography, crystallization, electrofocusing, or preparative gel electrophoresis, are well known and widely used in the art.

Alternatively, proteins, fusion proteins, or polypeptides of the invention can be produced by recombinant DNA methods or by synthetic chemical methods. Synthetic chemistry methods, such as solid phase peptide synthesis, can be used to synthesize proteins, fusion proteins, or polypeptides. For production of recombinant proteins, fusion proteins, or polypeptides, coding sequences selected from the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19 can be expressed in prokaryotic or eukaryotic host cells using expression systems known in the art. These expression systems include bacterial, yeast, insect, and mammalian cells (see below).

The resulting expressed protein can then be purified from the culture medium or from extracts of the cultured cells using purification procedures known in the art. For example, for proteins fully secreted into the culture medium, cell-free medium can be diluted with sodium acetate and contacted with a cation exchange resin, followed by hydrophobic interaction chromatography. Using this method, the desired protein, fusion protein, or polypeptide is typically greater than 95% pure.

Further purification can be undertaken, using, for example, any of the techniques listed above. Proteins, fusion proteins, or polypeptides can also be tagged with an epitope, such as a "Flag" epitope (Kodak), and purified using an antibody which specifically binds to that epitope.

5           It may be necessary to modify a protein produced in yeast or bacteria, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain a functional protein. Such covalent attachments can be made using known chemical or enzymatic methods.

10           Proteins or polypeptides of the invention can also be expressed in cultured cells in a form which will facilitate purification. For example, a secreted protein or polypeptide can be expressed as a fusion protein comprising, for example, maltose binding protein, glutathione-S-transferase, or thioredoxin, and purified using a commercially available kit. Kits for expression and purification of such fusion proteins are available from companies such as New England BioLabs, Pharmacia,  
15           and Invitrogen.

          The coding sequences disclosed herein can also be used to construct transgenic animals, such as cows, goats, pigs, or sheep. Female transgenic animals can then produce proteins, polypeptides, or fusion proteins of the invention in their milk. Methods for constructing such animals are known and widely used in the art.

20           Isolated proteins, polypeptides, or fusion proteins of the invention can be used to obtain a preparation of antibodies which specifically bind to epitopes comprising amino acid sequences of the invention. Antibodies of the invention can be used, for example, to detect proteins, polypeptides, or fusion proteins of the invention which are secreted into culture medium or to identify tissues or cells  
25           which express these molecules. The antibodies can be polyclonal or monoclonal or can be single chain antibodies. Techniques for raising polyclonal and monoclonal antibodies and for constructing single chain antibodies are well known in the art.

          Antibodies of the invention bind specifically to epitopes comprising amino acid sequences of the invention, preferably to epitopes not present on other  
30           proteins. Typically a minimum number of contiguous amino acids to encode an epitope is 6, 8, or 10. However, more amino acids can be part of an epitope, for

example, at least 15, 25, or 50, especially to form epitopes which involve non-contiguous residues. Specific binding antibodies do not detect other proteins on Western blots of proteins or in immunocytochemical assays. Specific binding antibodies provide a signal at least ten-fold lower than the signal provided with epitopes which do not comprise amino acid sequences of the invention. Antibodies which bind specifically to secreted proteins of the invention include those that bind to mature or full-length proteins, to polypeptides or degradation products, to fusion proteins, or to protein variants. In a preferred embodiment of the invention, the antibodies immunoprecipitate the desired protein, fusion protein, or polypeptide from solution and react with the protein, fusion protein, or polypeptide on Western blots of polyacrylamide gels.

Techniques for purifying antibodies are those which are available in the art. In a preferred embodiment, antibodies are affinity purified by passing the antibodies over a column to which amino acid sequences of the invention are bound. The bound antibody is then eluted, for example using a buffer with a high salt concentration. Any such technique may be chosen to purify antibodies of the invention.

The invention also provides DNA constructs, for expressing all or a portion of a protein of the invention in a host cell. The DNA construct comprises a promoter which is functional in the particular host cell selected. The skilled artisan can readily select an appropriate promoter from the large number of cell type-specific promoters known and used in the art. The DNA construct can also contain a transcription terminator which is functional in the host cell.

The expression construct comprises a polynucleotide segment which encodes all or a portion of a human protein encoded by SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19 or a variant thereof. The polynucleotide segment is located downstream from the promoter. Transcription of the polynucleotide segment initiates at the promoter. DNA constructs can be linear or circular and can contain sequences, if desired, for autonomous replication.

The host cell comprising the DNA construct can be any suitable prokaryotic or eukaryotic cell. Expression systems in bacteria include those described in Chang

*et al.*, *Nature* (1978) 275: 615; Goeddel *et al.*, *Nature* (1979) 281: 544; Goeddel *et al.*, *Nucleic Acids Res.* (1980) 8: 4057; EP 36,776; U.S. 4,551,433; deBoer *et al.*, *Proc. Natl. Acad. Sci. USA* (1983) 80: 21-25; and Siebenlist *et al.*, *Cell* (1980) 20: 269.

5           Expression systems in yeast include those described in Hinnen *et al.*, *Proc. Natl. Acad. Sci. USA* (1978) 75: 1929; Ito *et al.*, *J. Bacteriol.* (1983) 153: 163; Kurtz *et al.*, *Mol. Cell. Biol.* (1986) 6: 142; Kunze *et al.*, *J. Basic Microbiol.* (1985) 25: 141; Gleeson *et al.*, *J. Gen. Microbiol.* (1986) 132: 3459; Roggenkamp *et al.*, *Mol. Gen. Genet.* (1986) 202 :302); Das *et al.*, *J. Bacteriol.* (1984) 158: 1165; De Louvencourt *et al.*, *J. Bacteriol.* (1983) 154: 737, Van den Berg *et al.*, *Bio/Technology* (1990) 8: 135; Kunze *et al.*, *J. Basic Microbiol.* (1985) 25: 141; Cregg *et al.*, *Mol. Cell. Biol.* (1985) 5: 3376; U.S. 4,837,148; U.S. 4,929,555; Beach and Nurse, *Nature* (1981) 300: 706; Davidow *et al.*, *Curr. Genet.* (1985) 10: 380; Gaillardin *et al.*, *Curr. Genet.* (1985) 10: 49; Ballance *et al.*, *Biochem. Biophys. Res. Commun.* (1983) 112: 284-289; Tilburn *et al.*, *Gene* (1983) 26: 205-22;; Yelton *et al.*, *Proc. Natl. Acad. Sci. USA* (1984) 81: 1470-1474; Kelly and Hynes, *EMBO J.* (1985) 4: 475479; EP 244,234; and WO 91/00357.

15           Expression of heterologous genes in insects can be accomplished as described in U.S. 4,745,051; Friesen *et al.* (1986) "The Regulation of Baculovirus Gene Expression" in: THE MOLECULAR BIOLOGY OF BACULOVIRUSES (W. Doerfler, ed.); EP 127,839; EP 155,476; Vlak *et al.*, *J. Gen. Virol.* (1988) 69: 765-776; Miller *et al.*, *Ann. Rev. Microbiol.* (1988) 42: 177; Carbonell *et al.*, *Gene* (1988) 73: 409; Maeda *et al.*, *Nature* (1985) 315: 592-594; Lebacq-Verheyden *et al.*, *Mol. Cell. Biol.* (1988) 8: 3129; Smith *et al.*, *Proc. Natl. Acad. Sci. USA* (1985) 82: 8404; Miyajima *et al.*, *Gene* (1987) 58: 273; and Martin *et al.*, *DNA* (1988) 7:99. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts are described in Luckow *et al.*, *Bio/Technology* (1988) 6: 47-55, Miller *et al.*, in GENERIC ENGINEERING (Setlow, J.K. *et al.* eds.), Vol. 8 (Plenum Publishing, 1986), pp. 277-279; and Maeda *et al.*, *Nature*, (1985) 315: 592-594.

25           Mammalian expression can be accomplished as described in Dijkema *et al.*,

30

*EMBO J.* (1985) 4: 761; Gorman *et al.*, *Proc. Natl. Acad. Sci. USA* (1982b) 79: 6777; Boshart *et al.*, *Cell* (1985) 41: 521; and U.S. 4,399,216. Other features of mammalian expression can be facilitated as described in Ham and Wallace, *Meth. Enz.* (1979) 58: 44; Barnes and Sato, *Anal. Biochem.* (1980) 102: 255; U.S. 4,767,704; U.S. 4,657,866; U.S. 4,927,762; U.S. 4,560,655; WO 90/103430, WO 87/00195, and U.S. RE 30,985.

DNA constructs of the invention can be introduced into host cells using any technique known in the art. These techniques include transferrin-polycation-mediated DNA transfer, transfection with naked or encapsulated nucleic acids, liposome-mediated cellular fusion, intracellular transportation of DNA-coated latex beads, protoplast fusion, viral infection, electroporation, and calcium phosphate-mediated transfection.

Alternatively, expression of an endogenous gene encoding a protein of the invention can be manipulated by introducing by homologous recombination a DNA construct comprising a transcription unit in frame with the endogenous gene, to form a homologously recombinant cell comprising the transcription unit. The transcription unit comprises a targeting sequence, a regulatory sequence, an exon, and an unpaired splice donor site. The new transcription unit can be used to turn the endogenous gene on or off as desired. This method of affecting endogenous gene expression is taught in U.S. 5,641,670, which is incorporated herein by reference.

The targeting sequence is a segment of at least 10, 12, 15, 20, or 50 contiguous nucleotides selected from the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19. The transcription unit is located upstream to a coding sequence of the endogenous gene. The exogenous regulatory sequence directs transcription of the coding sequence of the endogenous gene.

Secreted proteins of the invention have a variety of uses. For example, secreted proteins can be used in assays to determine biological activities, such as cytokine, cell proliferation, or cellular differentiation activities, tissue growth or

regeneration, activin or inhibin activity, chemotactic or chemokinetic activity, hemostatic or thrombolytic activity, receptor/ligand activity, tumor inhibition, or anti-inflammatory activity. Assays for these activities are known in the art and are disclosed, for example, in U.S. 5,654,173, which is incorporated herein by reference.

Proteins of the invention can also be used as biomarkers, to identify tissues or cell types which express the proteins, or a stage- or disease-specific alteration in protein expression. Proteins of the invention can be used in protein interaction assays, to identify ligands or binding proteins. Compounds which affect the biological activities of the secreted proteins or their ability to interact with specific ligands can be identified using proteins of the invention in screening assays. Proteins and antibodies of the invention can also be used to design diagnostic tests and therapeutic compositions for diseases which may be associated with altered expression of these proteins. Fusion proteins comprising, for example, signal sequences or transmembrane domains of the disclosed proteins, can be used to target other protein domains to cellular locations in which the domains are not normally found, such as bound to a cellular membrane or secreted extracellularly.

Further objects, features, and advantages of the present invention will readily occur to the skilled artisan provided with the disclosure above.

## SYNOPSIS OF THE INVENTION

1. An isolated and purified human protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

2. An isolated and purified human protein having an amino acid sequence which is at least 85% identical to an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

3. The isolated and purified human protein of item 2 wherein the amino acid sequence is at least 90% identical.

4. The isolated and purified human protein of item 2 wherein the amino acid sequence is at least 95% identical.

5 5. The isolated and purified human protein of item 2 wherein the amino acid sequence is at least 98% identical.

6. An isolated and purified human polypeptide comprising at least 6 contiguous amino acids of an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24,  
10 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

7. A fusion protein comprising a first protein segment and a second protein segment fused together by means of a peptide bond, wherein the first protein segment consists of at least 6 contiguous amino acids selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23,  
15 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

8. A preparation of antibodies which specifically bind to the human protein of item 1.

9. The preparation of antibodies of item 8 wherein the antibodies are monoclonal.

20 10. The preparation of antibodies of item 8 wherein the antibodies are polyclonal.

11. The preparation of antibodies of item 8 wherein the antibodies are single chain antibodies.

25 12. An isolated and purified subgenomic polynucleotide having a nucleotide sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19.

13. An isolated and purified subgenomic polynucleotide consisting of at least 10 contiguous nucleotides of a nucleotide sequence selected from the group



consisting of the nucleotide sequences shown in SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19.

14. An isolated gene corresponding to a cDNA sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19.

15. A DNA construct for expressing all or a portion of a human protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos: 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38, comprising:

a promoter; and

a polynucleotide segment encoding at least 6 contiguous amino acids of the human protein, wherein the polynucleotide segment is located downstream from the promoter, wherein transcription of the polynucleotide segment initiates at or 3' to the promoter.

16. A host cell comprising a DNA construct comprising:

a promoter; and

a polynucleotide segment encoding at least 6 contiguous amino acids of a human protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos: 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38, wherein the polynucleotide segment is located downstream from the promoter and wherein transcription of the polynucleotide segment initiates at or 3' to the promoter.

17. A homologously recombinant cell having incorporated therein a new transcription initiation unit, wherein the new transcription initiation unit comprises in 5' to 3' order:

(a) an exogenous regulatory sequence;

(b) an exogenous exon; and

(c) a splice donor site,

wherein the transcription initiation unit is located upstream to a coding sequence of a gene, wherein the gene comprises a nucleotide sequence selected from the group

consisting of the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19, and wherein the exogenous regulatory sequence controls transcription of the coding sequence of the gene.

18. A method of producing a human protein, comprising the steps of:

5

growing a culture of a cell comprising a DNA construct comprising

(1) a promoter and (2) a polynucleotide segment encoding at least 6 contiguous amino acids of a human protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38, wherein the polynucleotide segment is located downstream from the promoter and wherein transcription of the polynucleotide segment initiates at or 3' to the promoter; and;

10

purifying the protein from the culture.

19. A method of producing a human protein, comprising the steps of:

15

growing a culture of a homologously recombinant cell having incorporated therein a new transcription initiation unit, wherein the new transcription initiation unit comprises in 5' to 3' order:

(a) an exogenous regulatory sequence;

(b) an exogenous exon; and

(c) a splice donor site,

20

wherein the transcription initiation unit is located upstream to a coding sequence of a gene, wherein the gene comprises a nucleotide sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19 and wherein the exogenous regulatory sequence controls transcription of the coding sequence of the gene; and

25

purifying the protein from the culture.

20. A method of identifying a secreted polypeptide which is modified by rough microsomes, comprising the steps of:

transcribing *in vitro* a population of cDNA molecules whereby a population of cRNA molecules is formed;

translating a first portion of the population of cRNA molecules *in vitro* in the absence of rough microsomes whereby a first population of polypeptides is formed;

5 translating a second portion of the population of cRNA molecules *in vitro* in the presence of rough microsomes whereby a second population of polypeptides is formed;

comparing the first population of polypeptides with the second population of polypeptides; and

10 detecting polypeptide members of the second population which have been modified by the rough microsomes.

21. The method of item 20 wherein the population of cDNA molecules is synthesized by reverse transcription of a population of mRNA molecules.

22. The method of item 21 wherein the mRNA molecules are isolated from a mammal.

15 23. The method of item 22 wherein the mRNA molecules are isolated from a human.

24. The method of item 20 wherein the population of cDNA molecules is obtained from a cDNA library.

20 25. The method of item 24 wherein the cDNA library is derived from a mammalian genome.

26. The method of item 25 wherein the cDNA library is derived from a human genome.

## SEQUENCE LISTING

## (1) GENERAL INFORMATION

(i) APPLICANT: Chiron Corporation

(ii) TITLE OF THE INVENTION: Secreted Human Proteins

(iii) NUMBER OF SEQUENCES: 38

## (iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Banner &amp; Witcoff

(B) STREET: 1001 G Street, NW

(C) CITY: Washington

(D) STATE: DC

(E) COUNTRY: USA

(F) ZIP: 20001

## (v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Diskette

(B) COMPUTER: IBM Compatible

(C) OPERATING SYSTEM: DOS

(D) SOFTWARE: FastSEQ for Windows Version 2.0

## (vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:

(B) FILING DATE: 11-DEC-1997

## (C) CLASSIFICATION:

## (vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 60/032757

(B) FILING DATE: 11-DEC-1996

## (viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Kagan, Sarah A

(B) REGISTRATION NUMBER: 32141

(C) REFERENCE/DOCKET NUMBER:

2441.39505;1369.002;1452.001

## (ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 202-508-9100

(B) TELEFAX: 202-508-9299

(C) TELEX:

## (2) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2063 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (ix) FEATURE:

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GAATTCGGCA CGAGGCCTCA GTCTTCCAGG GCGGCGGTGG GTGTCCGCTT CTCTCTGCTC	60
TTCGACTGCA CCGCACTCGC GCGTGACCCT GACTCCCCCT AGTCAGCTCA GCGGTGCTGC	120
CATGCCGTGG CGCCGGCCCG AAGCCGGCGT CCGGGCTCGC GCCGTGTTGG CTCTGCCGTT	180
GCTCGCCCTG GCCCTGTGCG TGCCCGGGGC CCGGGGCCGG GCTCTCGAGT GGTTCCTGGC	240

CGTGGTAAAC ATCGAGTACG TGGACCCGCA GACCAACCTG ACGGTGTGGA GCGTCTCGGA	300
GAGTGGCCGC TTCGGCGACA GCTCGCCCAA GGAGGGCGCG CATGGCCTGG TGGGCGTCCC	360
GTGGGCGCCC GCGGAGAGACC TCGAGGGCTG CGCGCCCGAC ACGCGCTTCT TCGTGCCCGA	420
GCCCCGCGGC CGAGGGGCGG CGCCCTGGGT CGCCCTGGTG GCTCGTGGGG GCTGCACCTT	480
CAAGGACAAG GTGCTGGTGG CGGCGCGGAG GAACGCCTCG GCCGTGCTCC TCTACAATGA	540
GGAGCGCTAC GGGAAACATCA CCTTGCCCAT GTCTCACGCG GGAACAGGAA ATATAGTGGT	600
CATTATGATT AGCTATCCAA AAGGAAGAGA AATTTTGGAG CTGGTGCAAA AAGGAATTCC	660
AGTAACGATG ACCATAGGGG TTGGCACCCG GCATGTACAG GAGTTCATCA GCGGTCAGTC	720
TGTGGTGTIT GTGGCCATTG CCTTCATCAC CATGATGATT ATCTCGTTAG CCTGGCTAAT	780
ATTTTACTAT ATACAGCGTT TCCTATATAC TGGCTCTCAG ATTGGAAGTC AGAGCCATAG	840
AAAAGAACT AAGAAAGTTA TTGGCCAGCT TCTACTTCAT ACTGTAAAGC ATGGAGAAAA	900
GGGAATTGAT GTTGATGCTG AAAATTGTGC AGTGTGTATT GAAAATTTCA AAGTAAAGGA	960
TATTATTAGA ATTCTGCCAT GCAAGCATAT TTTTCATAGA ATATGCATTG ACCCATGGCT	1020
TTTGATCAC CGAACATGTC CAATGTGTAA ACTTGATGTC ATCAAAGCCC TAGGATATTG	1080
GGGAGAGCCT GGGGATGTAC AGGAGATGCC TGCTCCAGAA TCTCCTCTG GAAGGGATCC	1140
AGCTGCAAAAT TTGAGTCTAG CTTTACCAGA TGATGACGGA AGTGATGACA GCAGTCCACC	1200
ATCAGCCTCC CCTGCTGAAT CTGAGCCACA GTGTGATCCC AGCTTTAAAG GAGATGCAGG	1260
AGAAAATACG GCATTGCTAG AAGCCGGCAG GAGTGACTCT CGGCATGGAG GACCCATCTC	1320
CTAGCACACG TGCCCACTGA AGTGGCACCA ACAGAAGTTT GGCTTGAAT AAAGGACATT	1380
TTATTTTTTT TACTTTAGCA CATAATTTGT ATATTTGAAA ATAATGTATA TTATTTTACC	1440
TATTAGATTC TGATTGATA TACAAAGGAC TAAGATATTT TCTTCTTGAA GAGACTTTTC	1500
GATTAGTCCT CATATATTTA TCTACTAAAA TAGAGTGTIT ACCATGAACA GTGTGTTGCT	1560
TCAGACTATT ACAAAGACAA CTGGGGCAGG TACTCTAATA TAAAGGACAG GTGGTGTTC	1620
TAAATAATTG GCTGCTATGG TTCTGTAAAA ACCAGTTAAT TCTATTTTTC AAGGTTTTTG	1680
GCAAAGCACA TCAATGTTAG ACTAGTTGAA GTGGAATTGT ATAATTCAAT TCGATAATTG	1740
ATCTCATGGG CTTTCCCTGG AGGAAAGGTT TTTTTTGTG TTTTTTTTTT AAGAACTTGA	1800
AACTTGTAAG CTGAGATGTC TGTAGCTTTT TTGCCATCT GTAGTGATG TGAAGATTTC	1860
AAAACCTGAG AGCACTTTTT CTTGTTTtag AATTATGAGA AAGGCACTAG ATGACTTTAG	1920
GATTTGCAAT TTTCCCTTTA TTGCCTCATT TCTGTGACG CCTGTGTGGG GAGGGAAATC	1980
TGTTTATTTT TTCCTACAAA TAAAAAGCTA AGATTCTATA TCGCAAAAAA AAAAAAAAAA	2040
AAAAAAAAAA TTCCTGCGGC CGC	2063

## (2) INFORMATION FOR SEQ ID NO:2:

## (1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1328 base pairs

- (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

GAATTCGGCA CGAGGTAGGC AAGGGATAAA AAGGCACCTA AGGCCCTTTT GCAATAAGAA	60
GCCAGATGGA TAAAGGAAGT GCTGGTCACC CTGGAGGTGT ACTGGTTTGG GGAAGGTCCC	120
CGGCCCCCAC AGCCCTCTGG GGAGCCTCAC CCTGGCTCTC CCCACTCACC TCAGCCCTCA	180
GGCAGCCCTT CCACAGGGCC CCTCTCCTGC CTGGACAGCT CTGCTGGTCT CCCCCTCCCC	240
TGGAGAAGAA CAAGGCCATG GGTCCGCCCC TGCTGCTGCC CCTGCTGCTC CTGCTGCAGC	300
CGCCAGCATT TCTGCAGCCT GGTGGCTCCA CAGGATCTGG TCCAAGCTAC CTTTATGGGG	360
TCACTCAACC AAAACACCTC TCAGCCTCCA TGGGTGGCTC TGTGGAAATC CCCTTCTCCT	420
TCTATTACCC CTGGGAGTTA GCCATAGTTC CCAACGTGAG AATATCCTGG AGACGGGGCC	480
ACTTCCACGG GCAGTCCTTC TACAGCACAA GGCCGCCTTC CATTACAAAG GATTATGTGA	540
ACCGGCTCTT TCTGAACTGG ACAGAGGGTC AGGAGAGCGG CTTCTCAGG ATCTCAAACC	600
TGCGGAAGGA GGACCACTCT GTGTATTCTT GCCGAGTCGA GCTGGACACC CGGAGATCAG	660
GGAGGCAGCA GTTGCACTCC ATCAAGGGGA CCAAACTCAC CATCACCAG GCTGTCACAA	720
CCACCACCAC CTGGAGGCCC AGCAGCACAA CCACCATAGC CGGCCTCAGG GTCACAGAAA	780
GCAAAGGGCA CTCAGAATCA TGGCACCTAA GTCTGGACAC TGCCATCAGG GTTGCACTGG	840
CTGTGCTGT GCTCAAAACT GTCATTTTGG GACTGCTGTG CCTCTCTCTC CTGTGGTGGA	900
GGAGAAGGAA AGGTAGCAGG GCGCCAAGCA GTGACTTCTG ACCAACAGAG TGTGGGGAGA	960
AGGGATGTGT ATTAGCCCCG GAGGACGTGA TGTGAGACCC GCTTGTGAGT CCTCCACACT	1020
CGTTCCCCAT TGCAAGATA CATGGAGAGC ACCCTGAGGA CCTTTAAAAG GCAAAGCCGC	1080
AAGGCAGAAG GAGGCTGGGT CCCTGAATCA CCGACTGGAG GAGAGTTACC TACAAGAGCC	1140
TTCATCCAGG AGCATCCACA CTGCAATGAT ATAGGAATGA GGTCTGAACT CCACTGAATT	1200
AAACCACTGG CATTTGGGGG CTGTTTATTA TAGCAGTGCA AAGAGTTCCT TTATCCTCCC	1260
CAAGGATGGA AAAATACAAT TTATTTTGCT TACCATAAAA AAAAAAAAAA AAAAATTCCT	1320
GCGGCCCGC	1328

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1689 base pairs  
 (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

GAATTCGGCA	CGAGGGCAAG	ATTCGATACA	AAACCAATGA	ACCTGTGTGG	GAGGAAAAC	60
TCACCTTCTT	CATTCACAAT	CCCAAGCGCC	AGGACCTTGA	AGTTGAGGTC	AGAGACGAGC	120
AGCACCAGTG	TTCCTGCGG	AACCTGAAGG	TCCCCCTCAG	CCAGCTGCTC	ACCAGTGAGG	180
ACATGACTGT	GAGCCAGCGC	TTCCAGCTCA	GTAACCTCGG	TCCAAACAGC	ACCATCAAGA	240
TGAAGATTGC	CCTGCGGGTG	CTCCATCTCG	AAAAGCGAGA	AAGGCCTCCA	GACCACCAAC	300
ACTCAGCTCA	AGTCAAACGT	CCCTCTGTGT	CCAAAGAGGG	GAGGAAAACA	TCCATCAAAT	360
CTCATATGTC	TGGGTCTCCA	GGCCCTGGTG	GCAGCAACAC	AGCTCCATCC	ACACCAGTCA	420
TTGGGGGCAG	TGATAAGCCT	GGTATGGAAG	AAAAGGCCCA	GCCCCCTGAG	GCCGGCCCTC	480
AGGGGCTGCA	CGACCTGGGC	AGAAGCTCCT	CCAGCCTCCT	GGCCTCCCCA	GGCCACATCT	540
CAGTCAAGGA	GGCGACCCCC	AGCATCGCCT	CGGACATCTC	GCTGCCCATC	GCCACCCAGG	600
AGCTGCGGCA	AAGGCTGAGG	CAGCTGGAAA	ACGGGACGAC	CCTGGGACAG	TCTCCACTGG	660
GGCAGATCCA	GCTGACCATC	CGGCACAGCT	CGCAGAGAAA	CAAGCTTATC	GTGGTCGTGC	720
ATGCCTGCAG	AAACCTCATT	GCCTTCTCTG	AAGACGGCTC	TGACCCCTAT	GTCCGCATGT	780
ATTTATTACC	AGACAAGAGG	CGGTCAGGAA	GGAGGAAAAC	ACACGTGTCA	AAGAAAACAT	840
TAAATCCAGT	GTTTGATCAA	AGCTTTGATT	TCAGTGTTTC	GTTACCAGAA	GTGCAGAGGA	900
GAACGCTCGA	CGTGCCCGTG	AAGAACAGTG	GCGGCTTCCT	GTCCAAAGAC	AAAGGGCTCC	960
TTGGCAAAGT	ATTGGTTGCT	CTGGCATCTG	AAGAACTTGC	CAAAGGCTGG	ACCCAGTGGT	1020
ATGACCTCAC	GGAAGATGGG	ACGAGGCCTC	AGGCGATGAC	ATAGCCGCAG	CAGGCAGGAG	1080
GCGTCCTCTT	CAGCGTAGCT	CTCCACCTCT	ACCCGGAACA	CACCCTCTCA	CAGACGTACC	1140
AATGTTATTT	TTATAATTTT	ATGGATTTAG	TTATACATAC	CTTAATAGTT	TTATAAAATT	1200
GTTGACATTT	CAGGCAAATT	TGGCCAATAT	TATCATTGAA	TTTTCTGTGT	TGGATTTCCT	1260
CTAGGATTTT	GCCAGTTCCT	ACAACGTGCA	GTAGGGCGGC	GGTAGCTCTT	GTGTCTGTGG	1320
ACTCTGCTCA	GCTGTGTCCG	TAGGAGTCGG	ATGTGTCTGT	GCTTTATTAT	GGCCTTGTTT	1380
ATATATCACT	GAGGTATACT	ATGCCATGTA	AATAGACTAT	TTTTTATAAT	CTTAACATGC	1440
TGGTTTAAAT	TCAGAAGGAA	ATAGATCAAG	GAAATATATA	TATTTTCTTC	TAAACTTAT	1500
TAAATTCGTG	TGACAAATAA	TCATTTTCAT	CTTGGCAGCA	AAAAGTCTC	AGTGACCTAT	1560
TTTGTGGTGT	TTCTTTTGA	AAAGAAAAGC	TGAAATATTA	TAAATGCTA	GTATGTTTCT	1620
GCCCATATG	AAAGATGAAA	TAAAGTATTC	AAAATATTAA	AAAAAAAAAA	AAAAAATTCC	1680
TGCGGCCGC						1689



## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1505 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```

GAATTCGGCA CGAGGAGCAG ATCTGCAAGA GTTTCGTTTA TGGAGGCTGC TTGGGCAACA      60
AGAACAATA CCTTCGGGAA GAAGAGTGCA TTCTAGCCTG TCGGGGTGTG CAAGGTGGGC      120
CTTTGAGAGG CAGCTCTGGG GCTCAGGCGA CTTTCCCCCA GGGCCCCTCC ATGGAAAGGC      180
GCCATCCAGT GTGCTCTGGC ACCTGTCAGC CCACCCAGTT CCGCTGCAGC AATGGCTGCT      240
GCATCGACAG TTTCTTGAG TGTGACGACA CCCCCAACTG CCCCAGCGCC TCCGACGAGG      300
CTGCCTGTGA AAAATACACG AGTGGCTTTG ACGAGCTCCA GCGCATCCAT TTCCCCAGCG      360
ACAAAGGGCA CTGCGTGGAC CTGCCAGACA CAGGACTCTG CAAGGAGAGC ATCCCGCGCT      420
GGTACTACAA CCCCTTCAGC GAACACTGCG CCCGCTTTAC CTATGGTGGT TGTACGGCA      480
ACAAGAACAA CTTTGAGGAA GAGCAGCAGT GCCTCGAGTC TTGTCGCGGC ATCTCCAAGA      540
AGGATGTGTT TGGCCTGAGG CGGGAAATCC CCATTCCCAG CACAGGCTCT GTGGAGATGG      600
CTGTGCGAGT GTTCTGCTG ATCTGCATTG TGGTGGTGGT AGCCATCTTG GGTACTGCT      660
TCTTCAAGAA CCAGAGAAAG GACTTCCACG GACACCACCA CCACCACCA CCCACCCCTG      720
CCAGCTCCAC TGTCTCCACT ACCGAGGACA CGGAGCACCT GGTCTATAAC CACACCACGC      780
GGCCCTCTG AGCCTGGGTC TCACCGGCTC TCACCTGGCC CTGCTTCCTG CTGCCAAGG      840
CAGAGGCCTG GGCTGGGAAA AACTTTGGAA CCAGACTCTT GCCTGTTTCC CAGGCCCACT      900
GTGCCTCAGA GACCAGGGCT CCAGCCCTC TTGGAGAAGT CTCAGCTAAG CTCACGTCCT      960
GAGAAAGCTC AAAGGTTTGG AAGGAGCAGA AAACCCTTGG GCCAGAAGTA CCAGACTAGA     1020
TGGACCTGCC TGCATAGGAG TTTGGAGGAA GTTGGAGTTT TGTTTCTCT GTTCAAAGCT     1080
GCCTGTCCCT ACCCATGGT GCTAGGAAGA GGAGTGGGGT GGTGTCAGAC CCTGGAGGCC     1140
CCAACCCTGT CCTCCCGAGC TCCTCTTCCA TGCTGTGCGC CCAGGGCTGG GAGGAAGGAC     1200
TTCCCTGTGT AGTTTGTGCT GTAAAGAGTT GCTTTTGTG TATTTAATGC TGTGGCATGG     1260
GTGAAGAGGA GGGGAAGAGG CCTGTTTGGC CTCTCTATCC TCTCTTCCTC TTCCCCCAAG     1320
ATTGAGCTCT CTGCCCTGA TCAGCCCCAC CCTGGCCTAG ACCAGCAGAC AGAGCCAGGA     1380
GAAGCTCAGC TGCATTCCGC AGCCCCCACC CCAAGGTTT TCCAACATCA CAGCCCAGCC     1440
CGCCCACTGG GTAATAAAAG TGTTTGTGG AAAAAAAAAA AAAAAAAAAA AAGTCCTGCC     1500

```

GCCGC

1505

## (2) INFORMATION FOR SEQ ID NO:5:

## (1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2002 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (x1) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GAATTCGGCA CGAGGGCCAT GGCCGGGCTA TCCC CGGGT CCGCGCGCGC ACTGCTCGCC	60
CCCCTGCTGG CGTCGACGCT GTTGGCGCTG CTCGTGTCCG CCGCGCGGGG TCGCGGCGGC	120
CGGGACCACG GGGACTGGGA CGAGGCCTCC CGGCTGCCGC CGCTACCACC CCGCGAGGAC	180
GCGGCGCGCG TGGCCCGCTT CGTGACGCAC GTCTCCGACT GGGGCGCTCT GGCCACCATC	240
TCCACGCTGG AGGCGGTGCG CGGCCGGCCC TTCGCGGACG TCCTCTCGCT CAGCGACGGG	300
CCCCCGGGCG CGGCGACGGG CGTGCCCTAT TTCTACCTGA GCCCGCTGCA GCTCTCCGTG	360
AGCAACCTGC AGGAGAATCC ATATGCTACA CTGACCATGA CTTTGGCACA GACCAACTTC	420
TGCAAGAAAC ATGGATTTGA TCCACAAAGT CCCCTTTGTG TTCACATAAT GCTGTCAGGA	480
ACTGTGACCA AGGTGAATGA AACAGAAATG GATATGCAA AGCATTTCGT ATTCAATCGA	540
CACCCTGAGA TGAAAACCTG GCCTTCCAGC CATAATTGGT TCTTTGCTAA GTTGAATATA	600
ACCAATATCT GGGTCCTGGA CTACTTTGGT GGACCAAAAA TCGTGACACC AGAAGAATAT	660
TATAATGTCA CAGTTCAGTG AAGCAGACTG TGGTGAATTT AGCAACACTT ATGAAGTTTC	720
TTAAAGTGGC TCATACACAC TTAAAAGGCT TAATGTTTCT CTGGAAGCG TCCCAGAATA	780
TTAGCCAGTT TTCTGTCACA TGCTGGTTTG TTTGCTTGCT TGTTTACTTG CTTGTTTACC	840
AATAGAGTTG ACCTGTTATT GGATTTCTCG GAAGATGTGG TAGCTACTTT TTCTCTATTT	900
TGAAGCCATT TTCGTAGAGA AATATCCTC ACTATAATCA AATAAGTTT GTCCCATCAA	960
TTCCAAAGAT GTTCCAGTG GTGCTCTGA AGAGGAATGA GTACCAGTTT TAAATTGCCC	1020
ATTGGCATTG GAAGGTAGTT GAGTATGTGT TCTTATTCC TAGAAGCCAC TGTGCTTGGT	1080
AGAGTGCAAT ACTCACCACA GCTGCCTCTT GAGCTGCCTG AGCCTGGTGC AAAAGGATTG	1140
GCCCCATTA TGGTGCTTCT GAATAAATCT TGCCAAGATA GACAAACAAT GATGAACTC	1200
AGATGGAGCT TCCTACTCAT GTTGATTAT GTCTCACAAT CCTGGGTATT GTTAATTCAA	1260
CATAGGGTGA AACTATTTCT GATAAAGAAC TTTTGAAAA CTTTTTATAC TCTAAAGTGA	1320
TACTCAGAAC AAAAGAAAGT CATAAACTC CTGAATTTAA TTTCCCCACC TAAGTCGAGA	1380

CAGTATTATC AAAACACATG TGCACACAGA TTATTTTTTG GCTCCAAAAC TGGATTGCAA	1440
AAGAAAGAGG AGAGATATTT TGTGTGTTCC TGGTATTCTT TTATAAGTAA AGTTACCCAG	1500
GCATGGACCA GCTTCAGCCA GGGACAAAAT CCCCTCCCAA ACCACTCTCC ACAGCTTTTT	1560
AAAAATACTT CTA CTCTTAA CAATTACCTA AGGTTCCTTC AAACCCCCC AACTCTTAAT	1620
AGCTTCTAGT GCTGCTACAA TCTAAGTCAG GTCACCAGAG GGAAGAGAAC ATGGCATTAA	1680
AAGAATCACA TCTTCAGAAG AGAAGACACT AATATTATTA CCCATATACA TGATTTCAGA	1740
AGATGACATA AGATTCCTCT TAAAGAGGAA ATGTCAGGAA TCAAGCCACT GAATCCTTAA	1800
AGAGAAAAGT TGAATATGAG TCATTGTGTC TGAAAACCTGC AAAGTGAAC TAACTGAGAT	1860
CCAGCAAACA GGTTCGTGTT AAGAAAAATA ATTTATACTA AATTTAGTAA AATGGACTTC	1920
TTATTCAAAG CATCAATAAT TAAAAGAATT ATTTTAAAAA AAAAAAAAAA AAAAAAAAAA	1980
AAAAAAAAAT TCCTGCGGCC GC	2002

## (2) INFORMATION FOR SEQ ID NO:6:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1322 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GAATTCGGCA CGAGGGCCAC GACTCTGCTG GCATTTCTTC TATAGCCACT GGAATCTGAT	60
CCTGATTGTC TTCCACTACT ACCAGGCCAT CACCACTCCG CCTGGGTACC CACCCCAGGG	120
CAGGAATGAT ATCGCCACCG TCTCCATCTG TAAGAAGTGC ATTTACCCCA AGCCAGCCCCG	180
AACACACCAC TGCAGCATCT GCAACAGGTG TGTGCTGAAG ATGGATCACC ACTGCCCCTG	240
GCTAAACAAT TGTGTGGGCC ACTATAACCA TCGGTACTTC TTCTCTTTCT GCTTTTTCAT	300
GACTCTGGGC TGTGTCTACT GCAGCTATGG AAGTTGGGAC CTTTCCGGG AGGCTTATGC	360
TGCCATTGAG AAAATGAAAC AGCTCGACAA GAACAACTA CAGGCGGTTG CCAACCAGAC	420
TTATCACCAG ACCCCACCAC CCACCTTCTC CTTTCGAGAA AGGATGACTC ACAAGAGTCT	480
TGTCTACCTC TGGTTCCTGT GCAGTTCTGT GGCATTGCC CTGGGTGCC TAACTGTATG	540
GCATGCTGTT CTCATCAGTC GAGGTGAGAC TAGCATCGAA AGGCACATCA ACAAGAAGGA	600
GAGACGTCGG CTACAGGCCA AGGGCAGAGT ATTTAGGAAT CCTTACAACT ACGGCTGCTT	660
GGACAACTGG AAGGTATTCC TGGGTGTGGA TACAGGAAGG CACTGGCTTA CTCGGGTGCT	720
CTTACCTTCT ACTCACTTGC CCCATGGGAA TGAATGAGC TGGGAGCCCC CTCCCTGGGT	780

GACTGCTCAC	TCAGCCTCTG	TGATGGCAGT	GTGAGCTGGA	CTGTGTCAGC	CACGACTCGA	840
GCACTCATTC	TGCTCCCTAT	GTTATTTCAA	GGGCCTCCAA	GGGCAGCTTT	TCTCAGAATC	900
CTTGATCAAA	AAGAGCCAGT	GGGCCTGCCT	TAGGGTACCA	TGCAGGACAA	TTCAAGGACC	960
AGCCTTTTTA	CCACTGCAGA	AGAAAGACAC	AATGTGGAGA	AATCTTAGGA	CTGACATCCC	1020
TTTACTCAGG	CAAACAGAAG	TTCCAACCCC	AGACTAGGGG	TCAGGCAGCT	AGCTACCTAC	1080
CTTGCCCACT	GCTGACCCGG	ACCTCCTCCA	GGATACAGCA	CTGGAGTTGG	CCACCACCTC	1140
TTCTACTTGC	TGTCTGAAAA	AACACCTGAC	TAGTACAGCT	GAGATCTTGG	CTTCTCAACA	1200
GGGCAAAGAT	ACCAGGCCTG	CTGCTGAGGT	CACTGCCACT	TCTCACATGC	TGCTTAAGGG	1260
AGCACAAATA	AAGGTATTGC	ATTTTTAAAA	AAAAAAAAAA	AAAAAAAAAT	TCCTGCGGCC	1320
GC						1322

## (2) INFORMATION FOR SEQ ID NO:7:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1573 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GAATTCGGCA	CGAGGAGCCT	GCCTTCATCT	AGGATGGCTC	CTCTGGGCAT	GCTGCTTGGG	60
CTGCTGATGG	CCGCCTGCTT	CACCTTCTGC	CTCAGTCATC	AGAACCTGAA	GGAGTTTGCC	120
CTGACCAACC	CAGAGAAGAG	CAGCACCAAA	GAAACAGAGA	GAAAAGAAAC	CAAAGCCGAG	180
GAGGAGCTGG	ATGCCGAAGT	CCTGGAGGTG	TTCCACCCGA	CGCATGAGTG	GCAGGCCCTT	240
CAGCCAGGGC	AGGCTGTCCC	TGCAGGATCC	CACGTACGGC	TGAATCTTCA	GACTGGGGAA	300
AGAGAGGCAA	AACTCCAATA	TGAGGACAAG	TTCCGAAATA	ATTGAAAGG	CAAAAGGCTG	360
GATATCAACA	CCAACACCTA	CACATCTCAG	GATCTCAAGA	GTGCACTGGC	AAAATTCAAG	420
GAGGGGGCAG	AGATGGAGAG	TTCAAAGGAA	GACAAGGCAA	GGCAGGCTGA	GGTAAAGCGG	480
CTCTTCCGCC	CCATTGAGGA	ACTGAAGAAA	GACTTTGATG	AGCTGAATGT	TGTCATTGAG	540
ACTGACATGC	AGATCATGGT	ACGGCTGATC	AACAAGTTCA	ATAGTTCCAG	CTCCAGTTTG	600
GAAGAGAAGA	TTGCTGCGCT	CTTTGATCTT	GAATATTATG	TCCATCAGAT	GGACAATGCG	660
CAGGACCTGC	TTTCTTTTGG	TGGTCTTCAA	GTGGTGATCA	ATGGGCTGAA	CAGCACAGAG	720
CCCCTCGTGA	AGGAGTATGC	TGCGTTTGTG	CTGGGCGCTG	CCTTTTCCAG	CAACCCCAAG	780
GTCCAGGTGG	AGGCCATCGA	AGGGGGAGCC	CTGCAGAAGC	TGCTGGTCAT	CCTGGCCACG	840

```

GAGCAGCCGC TCACTGCAAA GAAGAAGGTC CTGTTTGAC TGTGCTCCCT GCTGCGCCAC   900
TTCCCCTATG CCCAGCGGCA GTTCCTGAAG CTCGGGGGGC TGCAGGTCCT GAGGACCCTG   960
GTGCAGGAGA AGGGCACGGA GGTGCTCGCC GTGCGCGTGG TCACACTGCT CTACGACCTG  1020
GTCACGGAGA AGATGTTCCG CGAGGAGGAG GCTGAGCTGA CCCAGGAGAT GTCCCCAGAG  1080
AAGCTGCAGC AGTATCGCCA GGTACACCTC CTGCCAGGCC TGTGGGAACA GGGCTGGTGC  1140
GAGATCACGG CCCACCTCCT GGCCTGCCCC GAGCATGATG CCCGTGAGAA GGTGCTGCAG  1200
ACACTGGGCG TCCTCCTGAC CACCTGCCGG GACCGCTACC GTCAGGACCC CCAGCTCGGC  1260
AGGACACTGG CCAGCCTGCA GGCTGAGTAC CAGGTGCTGG CCAGCCTGGA GCTGCAGGAT  1320
GGTGAGGACG AGGGCTACTT CCAGGAGCTG CTGGGCTCTG TCAACAGCTT GCTGAAGGAG  1380
CTGAGATGAG GCCCCACACC AGGACTGGAC TGGGATGCCG CTAGTGAGGC TGAGGGGTGC  1440
CAGCGTGGGT GGGCTTCTCA GGCAGGAGGA CATCTTGCA GTGCTGGCTT GGCCATTAAA  1500
TGGAACCTG AAGGCCAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA  1560
TTCCTGCGGC CGC                                     1573

```

## (2) INFORMATION FOR SEQ ID NO:8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1185 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```

GAATTCGGCA CGAGGGGGCT TTAAGGGACA GCTGAGCCGG CAGGTGGCAG ATCAGATGTG   60
GCAGGCTGGG AAAAGACAAG CCTCCAGGGC CTTGAGCTTG TACGCCAACA TCGACATCCT   120
CAGACCCTAC TTGATGTGG AGCCTGCTCA GGTGCGAAGC AGGCTCCTGG AGTCCATGAT   180
CCCTATCAAG ATGGTCAACT TCCCCAGAA AATTGCAGGT GAACTCTATG GACCTCTCAT   240
GCTGGTCTTC ACTCTGGTTG CTATCCTACT CCATGGGATG AAGACGTCTG ACACATTAT   300
CCGGGAGGGC ACCCTGATGG GCACAGCCAT TGGCACCTGC TTCGGCTACT GGCTGGGAGT   360
CTCATCCTTC ATTTACTTCC TTGCCTACCT GTGCAACGCC CAGATCACCA TGCTGCAGAT   420
GTTGGCACTG CTGGGCTATG GCCTCTTTGG GCATTGCATT GTCCTGTTCA TCACCTATAA   480
TATCCACCTC CACGCCCTCT TCTACCTCTT CTGGCTGTTG GTGGGTGGAC TGTCCACACT   540
GCGCATGGTA GCAGTGTGG TGTCTCGGAC CGTGGGCCCC ACACAGCGGC TGCTCCTCTG   600
TGGCACCTG GCTGCCCTAC ACATGCTCTT CCTGCTCTAT CTGCATTTG CCTACCACAA   660

```

AGTGGTAGAG	GGGATCCTGG	ACACACTGGA	GGGCCCCAAC	ATCCCGCCCA	TCCAGAGGGT	720
CCCCAGAGAC	ATCCCTGCCA	TGCTCCCTGC	TGCTCGGCTT	CCCACCACCG	TCCTCAACGC	780
CACAGCCAAA	GCTGTTGCGG	TGACCCTGCA	GTCACACTGA	CCCCACCTGA	AATTCTTGGC	840
CAGTCCTCTT	TCCCCGAGCT	GCAGAGAGGA	GGAAGACTAT	TAAAGGACAG	TCCTGATGAC	900
ATGTTTCGTA	GATGGGGTTT	GCAGCTGCCA	CTGAGCTGTA	GCTGCGTAAG	TACCTCCTTG	960
ATGCCTGTGG	GCACTTCTGA	AAGGCACAAG	GCCAAGAACT	CCTGGCCAGG	ACTGCAAGGC	1020
TCTGCAGCCA	ATGCAGAAAA	TGGGTCAGCT	CCTTTGAGAA	CCCCTCCCCA	CCTACCCCTT	1080
CCTTCCTCTT	TATCTCTCCC	ACATTGTCTT	GCTAAATATA	GACTTGGTAA	TTAAAATGTT	1140
GATTGAAGTC	TGGAAAAAAA	AAAAAAAAAA	AATTCCTGCG	GCCGC		1185

## (2) INFORMATION FOR SEQ ID NO:9:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1226 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GAATTCGGCA	CGAGGCAAGC	CACCATCTTC	CTTCGGCCTG	CACCCCTTTA	AAGGCACCCA	60
GACCCCTCTG	GAAAAAGATG	AACTGAAGCC	CTTTGACATC	CTCCAGCCTA	AGGAGTACTT	120
CCAGCTCAGC	CGCCACACGG	TCATTAAGAT	GGGAAGTGAG	AACGAGGCCC	TGGATCTCTC	180
CATGAAGTCA	GTGCCCTGGC	TCAAGGCTGG	TGAAGTCAGT	CCCCCAATCT	TCCAGGAAGA	240
TGCAGCCCTA	GACCTGTCAG	TGGCAGCCCA	CCGGAATCC	GAGCCTCCCC	CTGAGACACT	300
GTATGACAGT	GGTGCATCAG	TGGACAGCTC	AGGTCACACA	GTGATGGAGA	AACTTCCCAG	360
TGGCATGGAA	ATTTCTTTTG	CCCCTGCCAC	GTCCCATGAG	GCCCCAGCCA	TGATGGATAG	420
TCACATCAGC	AGCAGTGATG	CTGCTACCGA	GATGCTCAGC	CAGCCCAACC	ACCCAGCGG	480
CGAAGTCAAG	GCTGAAAATA	ACATTGAGAT	GGTGGGCGAG	TCCCAGGCGG	CCAAGGTCAT	540
TGTCTCTGTC	GAAGATGCTG	TGCCTACCAT	ATTCTGTGGC	AAGATCAAAG	GCCTCTCAGG	600
GGTGTCCACC	AAAACTTCT	CCTTCAAAAG	AGAAGACTCC	GTGCTTCAGG	GCTATGACAT	660
CAACAGCCAA	GGGGAAGAGT	CCATGGGAAA	TGCAGAGCCC	CTTAGGAAAC	CCATCAAAAA	720
CCGGAGCATA	AAGTTAAAGA	AAGTGAAGTC	CCAGGAAGTA	CACATGCTCC	CAATCAAAAA	780
ACAACGGCTG	GCCACCTTTT	TTCCAAGAAA	GTAATAACG	GCTTTTAAA	ATTGTATGA	840
TTATAATATG	GGGAAAGGTG	CATTGGTTTT	ATAAAAAGGC	ATTTAAACA	AATTATCTTT	900

GTTAATTATT TTGGGGAGTA GTTGGGAAAT GGAAAGGTGA ATTGGCTCTA GAGGCCCTGT	960
ATGCTAGTAT CATTTTCTTT TTTAATTTT GACTTTTCAC AAATGAGTAA ATAAGAGCAA	1020
CCTATTTTTC AAGCAGATTG CACATTTTTC GCAGCTTTAA TGGAATATTG GGTGAATTAG	1080
AGGGGTAAAA AAAGCTATTT TCATTGCCAC AAAGTGCTTT GATGATGTAA TACCTAATAA	1140
AGGGTAGGAT GAATATTTCA CAATAAATGT TTGTTGCAC TAAAAAAAAA AAAAAAAAAA	1200
AAAAAAAAAA AAATTCCTGC GGCCGC	1226

## (2) INFORMATION FOR SEQ ID NO:10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1049 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GAATTCGGCA CGAGGGCGCC ATGGTGAAGG TGACGTTCAA CTCCGCTCTG GCCCAGAAGG	60
AGGCCAAGAA GGACGAGCCC AAGAGCGGCG AGGAGGCGCT CATCATCCCC CCCGACGCCG	120
TCGCGGTGGA CTGCAAGGAC CCAGATGATG TGGTACCAGT TGGCCAAAGA AGAGCCTGGT	180
GTTGGTGCAT GTGCTTTGGA CTAGCATTTA TGCTTGCAGG TGTTATTCTA GGAGGAGCAT	240
ACTTGTAACA ATATTTTGCA CTTCAACCAG ATGACGTGTA CTACTGTGGA ATAAAGTACA	300
TCAAAGATGA TGTCACTCTA AATGAGCCCT CTGCAGATGC CCCAGCTGCT CTCTACCAGA	360
CAATTGAAGA AAATATTAAA ATCTTTGAAG AAGAAGAAGT TGAATTTATC AGTGTGCCTG	420
TCCAGAGTT TGCAGATAGT GATCCTGCCA ACATTGTTCA TGACTTTAAC AAGAACTTA	480
CAGCCTATTT AGATCTTAAC CTGGATAAGT GCTATGTGAT CCCTCTGAAC ACTTCCATTG	540
TTATGCCACC CAGAAACCTA CTGGAGTTAC TTATTAACAT CAAGGCTGGA ACCTATTTGC	600
CTCAGTCCTA TCTGATTCAT GAGCACATGG TTATTACTGA TCGCATTGAA AACATTGATC	660
ACCTGGGTTT CTTTATTAT CGACTGTGTC ATGACAAGGA AACTTACAAA CTGCAACGCA	720
GAGAACTAT TAAAGGTATT CAGAAACGTG AAGCCAGCAA TTGTTTCGCA ATTCCGGCATT	780
TTGAAAACAA ATTTGCCGTG GAAACTTTAA TTTGTTCTTG AACAGTCAAG AAAACATTA	840
TTGAGGAAAA TTAATATCAC AGCATAACCC CACCCTTAC ATTTTGTGTC AGTTGATTAT	900
TTTTTAAAGT CTTCTTTCAT GTAAGTAGCA AACAGGGCTT TACTATCTTT TCATCTCATT	960
AATTCAATTA AAACCATTAC CTTAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA	1020
AAAAAAAAAA AAAAAATTCC TGCGGCCGC	1049

## (2) INFORMATION FOR SEQ ID NO:11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1142 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```

GAATTCGGCA CGAGGGGAGA ATACTTTTTC CGATGCCTAC TGGAGACTTT GATTTCGAAGC   60
CCAGTTGGGC CGACCAGGTG GAGGAGGAGG GGGAGGACGA CAAATGTGTC ACCAGCGAGC   120
TCCTCAAGGG GATCCCTCTG GCCACAGGTG ACACCAGCCC AGAGCCAGAG CTACTGCCGG   180
GAGCTCCACT GCCGCCTCCC AAGGAGGTCA TCAACGGAAA CATAAAGACA GTGACAGAGT   240
ACAAGATAGA TGAGGATGGC AAGAAGTCA AGATTGTCCG CACCTTCAGG ATTGAGACCC   300
GGAAGGCTTC AAAGCTGTG GCAAGGAGGA AGAAGTGGA GAAGTTCGGG AACTCAGAGT   360
TTGACCCCC CGGACCCAAT GTGGCCACCA CCACTGTCAG TGACGATGTC TCTATGACGT   420
TCATCACCAG CAAAGAGGAC CTGAAGTCCC AGGAGGAGGA GGACCCATG AACAAATTCA   480
AGGGCCAGAA GATCGTGTCC TGCCGCATCT GCAAGGGCGA CCACTGGACC ACCCGCTGCC   540
CCTACAAGGA TACGCTGGGG CCCATGCAGA AGGAGCTGGC CGAGCAGCTG GGCCTGTCTA   600
CTGGCGAGAA GGAGAAGCTG CCGGGAGAGC TAGAGCCGGT GCAGGCCACG CAGAACAAGA   660
CAGGGAAGTA TGTCCGCGCG AGCCTGCGCG ACGGGGCCAG CCGCCGCGGG GAGTCCATGC   720
AGCCCAACCG CAGAGCCGAC GACAACGCCA CCATCCGTGT CACCAACTTG CGCAGAGGAC   780
ACGCGTGAGA CCGACCTGCA GGAGCTCTTC CGGCCTTTTC GCTCCATCTC CCGCATCTAC   840
CTGGCTAAGG ACAAGACCAC TGGCCAATCC AAGGGCTTTG CCTTCATCAG CTTCCACCGC   900
CGCGAGGATG CTGCGCGTGC CATTGCCGGG GTGTCCGGCT TTGGCTACGA CCACCTCATC   960
CTCAACGTCG AGTGGGGCAA GCCGTCCACC AACTAAGCCA GCTGCCACTG TGTAATCGGT  1020
CCGGGACCCT TGGCGACAGA AGACAGCCTC CGAGAGCGCG GGCTCCAAGG GCAATAAAGC  1080
AGCTCCACTC TCAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAT TCCTGCGGCC  1140
GC                                     1142

```

## (2) INFORMATION FOR SEQ ID NO:12:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1696 base pairs



(B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GAATTCGGCA CGAGGGAAAC ATGGCGGTAG GCTGGGACCA TAACACAAGC ATGACTATAT	60
GAAGGAACAG GAAGGTTTTCTCTGAAGATGA GGCCTGAGTAA TCGGAAAAAA ACTTTAAGTT	120
TGGTAAAAGA GTTGGATGCC TTTCCGAAGG TTCCTGAGAG CTATGTAGAG ACTTCAGCCA	180
GTGGAGGTAC AGTTTCTCTA ATAGCATTTA CAACTATGGC TTTATTAACC ATAATGGAAT	240
TCTCAGTATA TCAAGATACA TGGATGAAGT ATGAATACGA AGTAGACAAG GATTTTTCTA	300
GCAAATTAAG AATTAATATA GATATTACTG TTGCCATGAA GTGTCAATAT GTTGGAGCGG	360
ATGTATTGGA TTAGCAGAA ACAATGGTTG CATCTGCAGA TGGTTTAGTT TATGAACCAA	420
CAGTATTGTA TCTTTCACCA CAGCAGAAAG AGTGGCAGAG GATGCTGCAG CTGATTCAGA	480
GTAGGCTACA AGAAGAGCAT TCACTTCAAG ATGTGATATT TAAAGTGCT TTTAAAAGTA	540
CATCAACAGC TCTTCCACCA AGAGAAGATG ATTCATCACA GTCTCCAAAT GCATGCAGAA	600
TTCATGGCCA TCTATATGTC AATAAAGTAG CAGGGAATTT TCACATAACA GTGGGCAAGG	660
CAATTCACCA TCCTCGTGGT CATGCACATT TGGCAGCACT TGTCAACCAT GAATCTTACA	720
ATTTTCTCA TAGAATAGAT CATTTGTCTT TTGGAGAGCT TGTTCCAGCA ATTATTAATC	780
CTTTAGATGG AACTGAAAAA ATTGCTATAG ATCACAACCA GATGTTCCAA TATTTTATTA	840
CAGTTGTGCC AACAAAACTA CATAATATA AATATCAGC AGACACCCAT CAGTTTTCTG	900
TGACAGAAAG GGAACGTATC ATTAACCATG CTGCAGGCAG CCATGGAGTC TCTGGGATAT	960
TTATGAAATA TGATCTCAGT TCTCTTATGG TGACAGTTAC TGAGGAGCAC ATGCCATTCT	1020
GGCAGTTTTT TGTAAGACTC TGTGGTATTG TTGGAGGAAT CTTTTCACCA ACAGGCATGT	1080
TACATGGAAT TGGAAAATTT ATAGTTGAAA TAATTTGCTG TCGTTTCAGA CTGGATCCT	1140
ATAAACCTGT CAATTCTGTT CCTTTTGAGG ATGGCCACAC AGACAACCAC TTACCTCTTT	1200
TAGAAAATAA TACACATTAA CACCTCCCGA TTGAAGGAGA AAAACTTTTT GCCTGAGACA	1260
TAAACCTTT TTTAATAAT AAAATATTGT GCAATATATT CAAAGAAAAG AAAACACAAA	1320
TAAGCAGAAA ACATACTTAT TTTAAAAAAG AAAAAAAGG ATAAAAAAC CCAAACTGAA	1380
ATTCTATATA CGTTGTGCT GTTACAAATG TCGTAGAAGA AATCATGCAG CTAAACGATG	1440
AAGAAGCCCA ACTGGAGTGT TGCTTTGAAG ATGACGCCTT CTTATATTTT CATAGCAAAT	1500
GGGTGGTATC AAAATCAGAC ATTGCTTCTT GCTGATAAAA AGCCTGAAGG AAATAAGTGA	1560
AACTACATCT ATGGGAAAAA AAAAAACATT GAGAAGTGCA AATGTTGCA TCCTTTTGT	1620
TTTAAAGAT ATGATGTCAG AATAAATGT GGAACATA CGRAAAAAA AAAAAAAA	1680
AAATTCCTGC GGCCGC	1696

## (2) INFORMATION FOR SEQ ID NO:13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1100 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAATTCGGCA CGAGGCGGCA CGAGGCGGCA CGAGGGTGGC ATATCACGGC CATGGGGTCT	60
CAGCATTCCG CTGCTGCTCG CCCCTCCTCC TGCAGGCGAA AGCAAGAAGA TGACAGGGAC	120
GGTTTGCTGG CTGAACGAGA GCAGGAAGAA GCCATTGCTC AGTTCCCATA TGTGGAATTC	180
ACCGGGAGAG ATAGCATCAC CTGTCTCAGC TGCCAGGGGA CAGGCTACAT TCCAACAGAG	240
CAAGTAAATG AGTTGGTGGC TTTGATCCCA CACAGTGATC AGAGATTGCG CCCTCAGCGA	300
ACTAAGCAAT ATGTCCTCCT GTCCATCCTG CTTTGTCTCC TGGCATCTGG TTTGGTGGTT	360
TTCTTCCTGT TTCCGCATTC AGTCCTTGTC GATGATGACG GCATCAAAGT GGTGAAAGTC	420
ACATTTAATA AGCAAGACTC CCTTGTAATT CTCACCATCA TGGCCACCCT GAAAATCAGG	480
AACTCCAAT TCTACACGGT GGCAGTGACC AGCCTGTCCA GCCAGATTCA GTACATGAAC	540
ACAGTGGTCA GTACATATGT GACTACTAAC GTCTCCCTTA TTCCACCTCG GAGTGAGCAA	600
CTGGTGAATT TTACCGGGAA GGCCGAGATG GGAGGACCGT TTTCCTATGT GTACTTCTTC	660
TGCACGGTAC CTGAGATCCT GGTGCACAAC ATAGTGATCT TCATGCGAAC TTCAGTGAAG	720
ATTTCATACA TTGGCCTCAT GACCCAGAGC TCCTTGGAGA CACATCACTA TGTGGATTGT	780
GGAGGAAATT CCACAGCTAT TTAACAACTG CTATTGGTTC TTCCACACAG CGCCTGTAGA	840
AGAGAGCACA GCATATGTTT CCAAGGCCTG AGTTCTGGAC CTACCCCCAC GTGGTGTAAAG	900
CAGAGGAGGA ATTGGTTCAC TTAATCCCA GCAAACATCC TCCTGCCACT TAGGAGGAAA	960
CACCTCCCTA TGGTACCATT TATGTTTCTC AGAACCAGCA GAATCAGTGC CTAGCCTGTG	1020
CCCAGCAAAT AGTTGGCACT CAATAAAGAT TTGCAGAATT TAAAAAAAAA AAAAAAAAAA	1080
AAAAAATTC CTGCGGCCCGC	1100

## (2) INFORMATION FOR SEQ ID NO:14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1588 base pairs
- (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GAATTCGGCA	CGAGGGTACC	TGCTTTTCTA	TTGCCTCTTT	GAAACAATGG	TCACGTGTTT	60
CCATGTTCCC	TACTCGGCTC	TCACCATGTT	CATCAGCACC	GAGCAGACTG	AGCGGGATTC	120
TGCCACCGCC	TATCGGATGA	CTGTGGAAGT	GCTGGGCACA	GTGCTGGGCA	CGGCGATCCA	180
GGGACAAATC	GTGGGCCAAG	CAGACACGCC	TTGTTTCCAG	GACCTCAATA	GCTCTACAGT	240
AGCTTCACAA	AGTGCCAACC	ATACACATGG	CACCACCTCA	CACAGGGAAA	CGCAAAAGGC	300
ATACCTGCTG	GCAGCGGGGG	TCATTGTCTG	TATCTATATA	ATCTGTGCTG	TCATCCTGAT	360
CCTGGGCGTG	CGGGAGCAGA	GAGAACCCTA	TGAAGCCCAG	CAGTCTGAGC	CAATCGCCTA	420
CTTCCGGGGC	CTACGGCTGG	TCATGAGCCA	CGGCCCATAC	ATCAAACCTA	TTACTGGCTT	480
CCTCTTCACC	TCCTTGGGCTT	TCATGCTGGT	GGAGGGGAAC	TTTGTCTTGT	TTTGACCTA	540
CACCTTGGGC	TTCCGCAATG	AATTCCAGAA	TCTACTCCTG	GCCATCATGC	TCTCGGCCAC	600
TTTAACCATT	CCCATCTGGC	AGTGGTTCTT	GACCCGGTTT	GGCAAGAAGA	CAGCTGTATA	660
TGTTGGGATC	TCATCAGCAG	TGCCATTTCT	CATCTTGGTG	GCCCTCATGG	AGAGTAACCT	720
CATCATTACA	TATGCGGTAG	CTGTGGCAGC	TGGCATCAGT	GTGGCAGCTG	CCTTCTTACT	780
ACCCTGGTCC	ATGCTGCCTG	ATGTCATTGA	CGACTTCCAT	CTGAAGCAGC	CCCACCTCCA	840
TGGAACCGAG	CCCATCTTCT	TCTCCTTCTA	TGTCTTCTTC	ACCAAGTTTG	CCTCTGGAGT	900
GTCACTGGGC	ATTCTTACCC	TCAGTCTGGA	CTTTGCAGGG	TACCAGACCC	GTGGCTGCTC	960
GCAGCCGGAA	CGTGTCAAGT	TTACACTGAA	CATGCTCGTG	ACCATGGCTC	CCATAGTTCT	1020
CATCCTGCTG	GGCCTGCTGC	TCTTCAAAT	GTACCCCAT	GATGAGGAGA	GGCGGCGGCA	1080
GAATAAGAAG	GCCCTGCAGG	CACTGAGGGA	CGAGGCCAGC	AGCTCTGGCT	GCTCAGAAAC	1140
AGACTCCACA	GAGCTGGCTA	GCATCCTCTA	GGGCCCGCCA	CCTTGCCCGA	AGCCACCATG	1200
CAGAAGGCCA	CAGAAGGGAT	CAGGACCTGT	CTGCCGGCTT	GCTGAGCAGC	TGGACTGCAG	1260
GTGCTAGGAA	GGGAAGTAA	GACTCAAGGA	GGTGGCCCAG	GACACTTGCT	GTGCTCACTG	1320
TGGGGCCGGC	TGCTCTGTGG	CCTCCTGCCT	CCCCTCTGCC	TGCCTGTGGG	GCCAAGCCCT	1380
GGGGCTGCCA	CTGTGAATAT	GCCAAGGACT	GATCGGGCCT	AGCCCGGAAC	ACTAATGTAG	1440
AAACCTTTTT	TTTACAGAGC	CTAATTAATA	ACTTAATGAC	TGTGTACATA	GCAATGTGTG	1500
TGTATGTATA	TGTCTGTGAG	CTATTAATGT	TATTAATTTT	CATAAAAGCT	GGAAGCAAA	1560
AAAAAAAAAA	AAAAATTCCT	GCGGCCGC				1588

(2) INFORMATION FOR SEQ ID NO:15:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1535 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```

GAATTCGGCA CGAGGCGGAA GTCCCGTCTC ACGGTTGCCC TGGCAGCGCG CGAGGCTGGT    60
GAGTCGGCAG CCCTGTGGCA GCCGGCGGGC TGGTTTCCAT GGTTCACGA TTAGGAACCA    120
CCAGCTGCTG CATCCCATGG CCAGGGGTGG CGTCCAGGTG GCAGAGCAGC TAGGAACGCA    180
AGGCCTGAAC CTGGGGGCCAG ACACCCTGCT CTCCCGGCCA TGGTCAACGA CCCTCCAGTA    240
CCTGCCTTAC TGTGGGCCCA GGAGGTGGGC CAAGTCTTGG CAGGCCGTGC CCGCAGGCTG    300
CTGCTGCAGT TTGGGGTGCT CTTCTGCACC ATCCTCCTTT TGCTCTGGGT GTCTGTCTTC    360
CTCTATGGCT CTTCTACTA TTCCTATATG CCGACAGTCA GCCACCTCAG CCCTGTGCAT    420
TTCTACTACA GGACCGACTG TGATTCTCC ACCACCTCAC TCTGCTCCTT CCCTGTTGCC    480
AATGTCTCGC TGAATAAGGG TGGACGTGAT CGGGTGCTGA TGTATGGACA GCCGTATCGT    540
GTTACCTTAG AGCTTGAGCT GCCAGAGTCC CCTGTGAATC AAGATTGGG CATGTTCTTG    600
GTCACCATT TCTGCTACAC CAGAGGTGGC CGAATCATCT CCACTTCTTC GCGTTCGGTG    660
ATGCTGCATT ACCGCTCAGA CCTGCTCCAG ATGCTGGACA CACTGGTCTT CTCTAGCCTC    720
CTGCTATTTG GCTTTGCAGA GCAGAAGCAG CTGCTGGAGG TGGAATCTA CGCAGACTAT    780
AGAGAGAAGT CGTACGTGCC GACCACTGGA GCGATCATTC AGATCCACAG CAAGCGCATC    840
CAGCTGTATG GAGCCTACCT CCGCATCCAC GCGCACTTCA CTGGGCTCAG ATACCTGCTA    900
TACAACTTCC CGATGACCTG CGCCTTCATA GGTGTTGCCA GCAACTTCAC CTTCTCAGC    960
GTCATCGTGC TCTTCAGCTA CATGCAGTGG GTGTGGGGGG GCATCTGGCC CCGACACCGC   1020
TTCTCTTTGC AGGTAAACAT CCGAAAAAGA GACAATTCCC GGAAGGAAGT CCAACGAAGG   1080
ATCTCTGCTC ATCAGCCAGG GCCTGAAGGC CAGGAGGAGT CAACTCCGCA ATCAGATGTT   1140
ACAGAGGATG GTGAGAGCCC TGAAGATCCC TCAGGGACAG AGGTCAGCTG TCCGAGGAGG   1200
AGAAACCAGA TCAGCAGCCC CTGAGCGGAG AAGAGGAGCT AGAGCCTGAG GCCAGTGATG   1260
GTTCAGGCTC CTGGGAAGAT GCAGCTTTGC TGACGGAGGC CAACCTGCCT GCTCCTGCTC   1320
CTGCTTCTGC TTCTGCCCCC GTCCTAGAGA CTCTGGGCAG CTCTGAACCT GCTGGGGGTG   1380
CTCTCCGACA GCGCCCCACC TGCTCTAGTT CCTGAAGAAA AGGGGCAGAC TCCTCACATT   1440
CCAGCACTTT CCCACCTGAC TCCTCTCCCC TCGTTTTTCC TTCAATAAAC TATTTTGTGT   1500
CAAAAAAAAA AAAAAAAAAA AATTCCTGCG GCCGC                                1535

```

## (2) INFORMATION FOR SEQ ID NO:16:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1322 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```

GAATTCGGCA CGAGGGCGGG CGCTACGGGC TTGACTCCCC CAAGGCCGAG GTCCGCGGCC      60
AGGTGCTGGC GCCGCTGCCC CTCCACGGAG TTGCTGATCA TCTGGGCTGT GATCCACAAA      120
CCCGGTTCTT TGTCCCTCCT AATATCAAAC AGTGGATTGC CTTGCTGCAG AGGGGAAACT      180
GCACGTTTAA AGAGAAAATA TCACGGGCCG CTTTCCACAA TGCAGTTGCT GTAGTCATCT      240
ACAATAATAA ATCCAAAGAG GAGCCAGTTA CCATGACTCA TCCAGGCACT GGAGATATTA      300
TTGCTGTCAT GATAACAGAA TTGAGGGGTA AGCATATTTT GAGTTATCTG GAGAAAAACA      360
TCTCTGTACA AATGACAATA GCTGTTGGAA CTCGAATGCC ACCGAAGAAC TTCAGCCGTG      420
GCTCTCTAGT CTTCGTGTCA ATATCCTTTA TTGTTTGTAT GATTATTTCT TCAGCATGGC      480
TCATATTCTA CTTCAATTCAA AAGATCAGGT ACACAAATGC ACGCGACAGG AACCAGCGTC      540
GTCTCGGAGA TGCAGCCAAG AAAGCCATCA GTAAATTGAC AACCAGGACA GTAAAGAAGG      600
GTGACAAGGA AACTGACCCA GACTTTGATC ATTGTGCAGT CTGCATAGAG AGCTATAAGC      660
AGAATGATGT CGTCCGAATT CTCCCCTGCA AGCATGTTT CCACAAATCC TCGGTGGATC      720
CCTGGCTTAG TGAACATTGT ACCTGTCTTA TGTGCAAACT TAATATATTG AAGGCCCTGG      780
GAATTGTGCC GAATTTGCCA TGTACTGATA ACGTAGCATT CGATATGGAA AGGCTCACCA      840
GAACCCAAGC TGTTAACCGA AGATCAGCCC TCGGCGACCT CGCCGGCGAC AACTCCCTTG      900
GCCTTGAGCC ACTTCCAAC TCGGGGATCT CACCTCTTCC TCAGGATGGG GAGCTCACTC      960
CGAGAACAGG AGAAATCAAC ATTGCAGTAA CAAAAGAATG GTTTATTATT GCCAGTTTTG      1020
GCCTCCTCAG TGCCCTCACA CTCTGTACA TGATCATCAG AGCCACAGCT AGCTTGAATG      1080
CTAATGAGGT AGAATGGTTT TGAAGAAGAA AAAACCTGCT TTCTGACTGA TTTTGCCTTG      1140
AAGGAAAAAA GAACCTATTT TTGTGCATCA TTTACCAATC ATGCCACACA AGCATTATT      1200
TTTAGTACAT TTTATTTTTT CATAAAATTG CTAATGCCAA AGCTTTGTAT TAAAAGAAAT      1260
AAATAATAAA ATAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAT TCCTGCGGCC      1320
GC                                                                                   1322

```

## (2) INFORMATION FOR SEQ ID NO:17:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1711 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```

GAATTCGGCA CGAGGCCCTC CCGCGCTCCC GGGGCGCGCG GGCCGCGCCC CCGACGCCCT 60
ACATATACTC AGGTGCGCCC CACCTGTCCG CCCGCACCTG CTGGCTCACC TCCGAGCCAC 120
CTCTGCTGCG CACCGCAGCC TCGGACCTAC AGCCCAGGAT ACTTTGGGAC TTGCCGGCGC 180
TCAGAAACGC GCCCAGACGG CCCCTCCACC TTTTGTTCG CTAGGGTCGC CGAGAGCGCC 240
CGGAGGGAAC CGCTTGGCCT TCGGGGACCA CCAATTTTGT CTGGAACCAC CCTCCCGGCG 300
TATCCTACTC CCTGTGCCGC GAGGCCATCG CTTCACTGGA GGGGTCGATT TGTGTGTAGT 360
TTGGTGACAA GATTTCATT CACCTGGCCC AAACCCCTTT TGTCTCTTTG GGTGACCGGA 420
AAACTCCACC TCAAGTTTTC TTTTGTGGGG CTGCCCCCCA AGTGTCTTT GTTTTACTGT 480
AGGGTCTCCC GCCCGGCGCC CCCAGTGTTT TCTGAGGCG GAAATGGCCA ATTCGGGCCCT 540
GCAGTTGCTG GGCTTCTCCA TGGCCCTGCT GGGCTGGGTG GGTCTGGTGG CCTGCACCGC 600
CATCCCGCAG TGGCAGATGA GCTCCTATGC GGGTGACAAC ATCATCACGG CCCAGGCCAT 660
GTACAAGGGG CTGTGGATGG ACTGCGTCAC GCAGAGCACG GGGATGATGA GCTGCAAAAT 720
GTACGACTCG GTGTCGCCCC TGTCCGCGGC CTTGCAGGCC ACTCGAGCCC TAATGGTGGT 780
CTCCCTGGTG CTGGGCTTCC TGGCCATGTT TGTGGCCACG ATGGGCATGA AGTGCACGCG 840
CTGTGGGGGA GACGACAAAG TGAAGAAGGC CCGTATAGCC ATGGGTGGAG GCATAATTTT 900
CATCGTGGCA GGTCTTGCCG CCTTGGTAGC TTGCTCCTGG TATGGCCATC AGATTGTCAC 960
AGACTTTTAT AACCTTTGA TCCCTACCAA CATTAAGTAT GAGTTTGGCC CTGCCATCTT 1020
TATTGGCTGG GCAGGGTCTG CCCTAGTCAT CCTGGGAGGT GCACTGCTCT CCTGTTCCCTG 1080
TCCTGGGAAT GAGAGCAAGG CTGGGTACCG TGCACCCCGC TCTTACCCTA AGTCCAACTC 1140
TTCCAAGGAG TATGTGTGAC CTGGGATCTC CTTGCCCCAG CCTGACAGGC TATGGGAGTG 1200
TCTAGATGCC TGAAGGGGCC TGGGGCTGAG CTCAGCCTGT GGGCAGGGTG CCGGACAAAG 1260
GCCTCCTGGT CACTCTGTCC CTGCACTCCA TGTATAGTCC TCTTGGGTTG GGGGTGGGGG 1320
GGTGCCGTTG GTGGGAGAGA CAAAAGAGG GAGAGTGTGC TTTTGTACA GTAATAAAAA 1380
ATAAGTATTG GGAAGCAGGC TTTTTCCTC TCAGGGCCTC TGCTTTCCTC CCGTCCAGAT 1440
CCTTGCAGGG AGCTTGAAC CTTAGTGCAC CTACTTCAGT TCAGAACACT TAGCACCCCA 1500
CTGACTCCAC TGACAATTGA CTAAAAGATG CAGGTGCTCG TATCTCGACA TTCATTCCCA 1560
CCCCCTCTT ATTTAAATAG CTACCAAAGT ACTTCTTTT TAATAAAAA ATAAAGATT 1620

```

TTATTAGGTA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1680  
AAAAAAAAAA AAAAAAATT CCTGCGGCCG C 1711

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1553 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GAATTCGGCA CGAGGGCAGG TCCAGAGTAA AGTCACTGAA GAGTGAAGC GAGGAAGGAA 60  
CAGGATGATT AGACCTCAGC TCGGACCGC GGGGCTGGA CGATGCCTCC TGCCGGGGCT 120  
GCTGCTGCTC CTGGTGCCCG TCCTCTGGGC CGGGGCTGAA AAGCTACATA CCCAGCCCTC 180  
CTGCCCCGCG GTCTGCCAGC CCACGCGCTG CCCC GCGCTG CCCACCTGCG CGCTGGGGAC 240  
CACGCCGGTG TTCGACCTGT GCCGCTGTTG CCGCGTCTGC CCCGCGGCCG AGCGTGAAGT 300  
CTGCGGCGGG GCGCAGGGCC AACCGTGCGC CCGGGGGCTG CAGTGCCTCC AGCCGCTGCG 360  
CCCCGGGTTC CCCAGCACCT GCGGTTGCCG GACGCTGGA GGGGCCGTGT GCGGCAGCGA 420  
CAGGCGCACC TACCCAGCA TGTGCGCGCT CCGGGCCGAA AACCGCGCCG CGCGCCGCTT 480  
GGGCAAGGTC CCGGCCGTGC CTGTGCAGTG GGGGAAGTGC GGGGATACAG GGACCAGAAG 540  
CGCAGGCCCG CTCAGGAGGA ATTACAACTT CATCGCCGCG GTGGTGAGA AGGTGGCGCC 600  
ATCGGTGGTT CACGTGCAGC TGTGGGGCAG GTTACTTCAC GGCAGCAGGC TTGTTCTCTG 660  
GTACAGTGGC TCTGGGTTCA TAGTGTCTGA GGACGGGCTC ATTATTACCA ATGCCCATGT 720  
TGTCAGGAAC CAGCAGTGGG TTGAGGTGGT GCTCCAGAAT GGGGCCCGTT ATGAAGCTGT 780  
TGTCAGGAT ATTGACCTTA AATTGGATCT TGCGGTGATT AAGATTGAAT CAAATGCTGA 840  
ACTTCCTGTA CTGATGCTGG GAAGATCATC TGACCTTCGG CTTGGAGAGT TTGTGGTGGC 900  
TTTGGGCAGC CCATTTTCTC TGCAGAACAC AGCTACTGCA GGAATTGTCA GCACCAAACA 960  
GCGAGGGGGC AAAGAACTGG GGATGAAGGA TTCAGATATG GACTACGTCC AGATTGATGC 1020  
CACAATTAAC TATGGGAATT CTGGTGGTCC TCTGGTGAAC TTGGATGGTG ATGTGATTGG 1080  
CGTCAATTCA TTGAGGGTGA CTGATGCAAT CTCCTTTGCA ATTCCTTCAG ATCGAGTTAG 1140  
GCAGTTCTTG GCAGAATACC ATGAGCACCA GATGAAAGGA AAGGCGTTTT CAAATAAGAA 1200  
ATATCTGGGT CTGCAAATGC TGTCCCTCAC TGTGCCCTT AGTGAAGAAT TGAAAATGCA 1260  
TTATCCAGAT TTCCCTGATG TGAGTTCTGG GGTTCATGTA TGTAAAGTGG TTGAAGGAAC 1320

AGCTGCTCAA AGCTCTGGAT TGAGAGATCA CGATGTAATT GTCAACATAA ATGGGAAACC	1380
TATTACTACT ACAACTGATG TTGTTAAAGC TCTTGACAGT GATTCCCTTT CCATGGCTGT	1440
TCTTCGGGGA AAAGATAATT TGCTCCTGAC AGTCATACCT GAAACAATCA ATTAAATATC	1500
TTGTTTTAAA GTGGGATTAT CTAAAAAAA AAAAAAAAAA TTCCTGCGGC CGC	1553

## (2) INFORMATION FOR SEQ ID NO:19:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1596 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GAATTCGGCA CGAGGGGAGC CGCTCCCGGA GCCCGGCCGT AGAGGCTGCA ATCGCAGCCG	60
GGAGCCCGCA GCCCGCGCCC CGAGCCCGCC GCCGCCCTTC GAGGGCGCCC CAGGCCGCGC	120
CATGGTGAAG GTGACGTTCA ACTCCGCTCT GGCCCAAGAG GAGGCCAAGA AGGACGAGCC	180
CGAGAGCGGC GAGGAGGCGC TCATCATCCC CCCCAGCGCC GTCGCGGTGG ACTGCAAGGA	240
CCCAGATGAT GTGGTACCAG TTGGCCAAAG AAGAGCCTGG TGTTGGTGCA TGTGCTTTGG	300
ACTAGCATT ATGCTTGACG GTGTTATTCT AGGAGGAGCA TACTTGTAACA AATATTTTGC	360
ACTTCAACCA GATGACGTGT ACTACTGTGG AATAAAGTAC ATCAAAGATG ATGTCATCTT	420
AAATGAGCCC TCTGCAGATG CCCCAGCTGC TCTCTACCAG ACAATTGAAG AAAATATTAA	480
AATCTTTGAA GAAGAAGAAG TTGAATTTAT CAGTGTGCCT GTCCCAGAGT TTGCAGATAG	540
TGATCCTGCC AACATTGTTT ATGACTTTAA CAAGAACTT ACAGCCTATT TAGATCTTAA	600
CCTGGATAAG TGCTATGTGA TCCCTCTGAA CACTTCCATT GTTATGCCAC CCAGAAACCT	660
ACTGGAGTTA CTTATTAACA TCAAGGCTGG AACCTATTTG CCTCAGTCCT ATCTGATTCA	720
TGAGCACATG GTTATTACTG ATCGCATTGA AAACATTGAT CACCTGGGTT TCTTTATTTA	780
TCGACTGTGT CATGACAAGG AACTTTACAA ACTGCACGCG AGAGAACTA TTAAAGGTAT	840
TCAGAAACGT GAAGCCAGCA ATTGTTTCGC AATTCGGCAT TTTGAAAACA AATTGCCGT	900
GGAAACTTTA ATTTGTTCTT GAACAGTCAA GAAAAACATT ATTGAGGAAA ATTAATATCA	960
CAGCATAACC CCACCTTTTA CATTTTGTGC AGTGATATTT TTTAAAGTCT CTTTCATGTA	1020
AGTAGCAAAC AGGGCTTTAC TATCTTTTCA TCTCATTAA TCAATTAAAA CCATTACCTT	1080
AAAATTTTTT TCTTTCGAAG TGTGGTGTCT TTTATATTTG AATTAGTAAC TGTATGAAGT	1140



```

CATAGATAAT AGTACATGTC ACCTTAGGTA GTAGGAAGAA TTACAATTTC TTAAATCAT 1200
TTATCTGGAT TTTTATGTTT TATTAGCATT TTCAAGAAGA CGGATTATCT AGAGAATAAT 1260
CATATATATG CATACGTAAA AATGGACCAC AGTGACTTAT TTGTAGTTGT TAGTTGCCCT 1320
GCTACCTAGT TTGTTAGTGC ATTTGAGCAC ACATTTTAAT TTTCTCTAA TTAAATGTG 1380
CAGTATTTTC AGTGCAAAT ATATTTAACT ATTAGAGAA TGATTCCAC CTTTATGTTT 1440
TAATATCCTA GGCATCTGCT GTAATAATAT TTTAGAAAAT GTTTGGAATT TAAGAAATAA 1500
CTTGTGTTAC TAATTTGTAT AACCCATATC TGTGCAATGG AATATAAATA TCACAAAGTT 1560
GTTTAAAAAA AAAAAAAAAA AAATTCCTGC GGCCGC 1596

```

## (2) INFORMATION FOR SEQ ID NO:20:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 400 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```

Met Ala Trp Arg Arg Arg Glu Ala Gly Val Gly Ala Arg Gly Val Leu
 1             5             10             15
Ala Leu Ala Leu Leu Ala Leu Ala Leu Cys Val Pro Gly Ala Arg Gly
      20             25             30
Arg Ala Leu Glu Trp Phe Ser Ala Val Val Asn Ile Glu Tyr Val Asp
      35             40             45
Pro Gln Thr Asn Leu Thr Val Trp Ser Val Ser Glu Ser Gly Arg Phe
      50             55             60
Gly Asp Ser Ser Pro Lys Glu Gly Ala His Gly Leu Val Gly Val Pro
65             70             75             80
Trp Ala Pro Gly Gly Asp Leu Glu Gly Cys Ala Pro Asp Thr Arg Phe
      85             90             95
Phe Val Pro Glu Pro Gly Gly Arg Gly Ala Ala Pro Trp Val Ala Leu
      100            105            110
Val Ala Arg Gly Gly Cys Thr Phe Lys Asp Lys Val Leu Val Ala Ala

```

115	120	125
Arg Arg Asn Ala Ser Ala Val Val Leu Tyr Asn Glu Glu Arg Tyr Gly		
130	135	140
Asn Ile Thr Leu Pro Met Ser His Ala Gly Thr Gly Asn Ile Val Val		
145	150	155
Ile Met Ile Ser Tyr Pro Lys Gly Arg Glu Ile Leu Glu Leu Val Gln		
165	170	175
Lys Gly Ile Pro Val Thr Met Thr Ile Gly Val Gly Thr Arg His Val		
180	185	190
Gln Glu Phe Ile Ser Gly Gln Ser Val Val Phe Val Ala Ile Ala Phe		
195	200	205
Ile Thr Met Met Ile Ile Ser Leu Ala Trp Leu Ile Phe Tyr Tyr Ile		
210	215	220
Gln Arg Phe Leu Tyr Thr Gly Ser Gln Ile Gly Ser Gln Ser His Arg		
225	230	235
Lys Glu Thr Lys Lys Val Ile Gly Gln Leu Leu Leu His Thr Val Lys		
245	250	255
His Gly Glu Lys Gly Ile Asp Val Asp Ala Glu Asn Cys Ala Val Cys		
260	265	270
Ile Glu Asn Phe Lys Val Lys Asp Ile Ile Arg Ile Leu Pro Cys Lys		
275	280	285
His Ile Phe His Arg Ile Cys Ile Asp Pro Trp Leu Leu Asp His Arg		
290	295	300
Thr Cys Pro Met Cys Lys Leu Asp Val Ile Lys Ala Leu Gly Tyr Trp		
305	310	315
Gly Glu Pro Gly Asp Val Gln Glu Met Pro Ala Pro Glu Ser Pro Pro		
325	330	335
Gly Arg Asp Pro Ala Ala Asn Leu Ser Leu Ala Leu Pro Asp Asp Asp		
340	345	350
Gly Ser Asp Asp Ser Ser Pro Pro Ser Ala Ser Pro Ala Glu Ser Glu		
355	360	365
Pro Gln Cys Asp Pro Ser Phe Lys Gly Asp Ala Gly Glu Asn Thr Ala		
370	375	380
Leu Leu Glu Ala Gly Arg Ser Asp Ser Arg His Gly Gly Pro Ile Ser		
385	390	395
		400

## (2) INFORMATION FOR SEQ ID NO:21:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 291 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```

Met Asp Lys Gly Ser Ala Gly His Pro Gly Gly Val Leu Val Trp Gly
 1           5           10           15
Arg Ser Pro Ala Pro Thr Ala Leu Trp Gly Ala Ser Pro Trp Leu Ser
          20           25           30
Pro Leu Thr Ser Ala Leu Arg Gln Pro Leu His Arg Ala Pro Leu Leu
          35           40           45
Pro Gly Gln Leu Cys Trp Ser Pro Arg Pro Leu Glu Lys Asn Lys Ala
          50           55           60
Met Gly Arg Pro Leu Leu Leu Pro Leu Leu Leu Leu Leu Gln Pro Pro
 65           70           75           80
Ala Phe Leu Gln Pro Gly Gly Ser Thr Gly Ser Gly Pro Ser Tyr Leu
          85           90           95
Tyr Gly Val Thr Gln Pro Lys His Leu Ser Ala Ser Met Gly Gly Ser
          100          105          110
Val Glu Ile Pro Phe Ser Phe Tyr Tyr Pro Trp Glu Leu Ala Ile Val
          115          120          125
Pro Asn Val Arg Ile Ser Trp Arg Arg Gly His Phe His Gly Gln Ser
          130          135          140
Phe Tyr Ser Thr Arg Pro Pro Ser Ile His Lys Asp Tyr Val Asn Arg
          145          150          155          160
Leu Phe Leu Asn Trp Thr Glu Gly Gln Glu Ser Gly Phe Leu Arg Ile
          165          170          175
Ser Asn Leu Arg Lys Glu Asp Gln Ser Val Tyr Phe Cys Arg Val Glu
          180          185          190

```

Leu Asp Thr Arg Arg Ser Gly Arg Gln Gln Leu Gln Ser Ile Lys Gly  
 195 200 205  
 Thr Lys Leu Thr Ile Thr Gln Ala Val Thr Thr Thr Thr Thr Trp Arg  
 210 215 220  
 Pro Ser Ser Thr Thr Thr Ile Ala Gly Leu Arg Val Thr Glu Ser Lys  
 225 230 235 240  
 Gly His Ser Glu Ser Trp His Leu Ser Leu Asp Thr Ala Ile Arg Val  
 245 250 255  
 Ala Leu Ala Val Ala Val Leu Lys Thr Val Ile Leu Gly Leu Leu Cys  
 260 265 270  
 Leu Leu Leu Leu Trp Trp Arg Arg Arg Lys Gly Ser Arg Ala Pro Ser  
 275 280 285  
 Ser Asp Phe  
 290

## (2) INFORMATION FOR SEQ ID NO:22:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 293 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met Thr Val Ser Gln Arg Phe Gln Leu Ser Asn Ser Gly Pro Asn Ser  
 1 5 10 15  
 Thr Ile Lys Met Lys Ile Ala Leu Arg Val Leu His Leu Glu Lys Arg  
 20 25 30  
 Glu Arg Pro Pro Asp His Gln His Ser Ala Gln Val Lys Arg Pro Ser  
 35 40 45  
 Val Ser Lys Glu Gly Arg Lys Thr Ser Ile Lys Ser His Met Ser Gly  
 50 55 60  
 Ser Pro Gly Pro Gly Gly Ser Asn Thr Ala Pro Ser Thr Pro Val Ile

65	70	75	80
Gly Gly Ser Asp Lys Pro Gly Met Glu Glu Lys Ala Gln Pro Pro Glu			
85	90	95	
Ala Gly Pro Gln Gly Leu His Asp Leu Gly Arg Ser Ser Ser Ser Leu			
100	105	110	
Leu Ala Ser Pro Gly His Ile Ser Val Lys Glu Pro Thr Pro Ser Ile			
115	120	125	
Ala Ser Asp Ile Ser Leu Pro Ile Ala Thr Gln Glu Leu Arg Gln Arg			
130	135	140	
Leu Arg Gln Leu Glu Asn Gly Thr Thr Leu Gly Gln Ser Pro Leu Gly			
145	150	155	160
Gln Ile Gln Leu Thr Ile Arg His Ser Ser Gln Arg Asn Lys Leu Ile			
165	170	175	
Val Val Val His Ala Cys Arg Asn Leu Ile Ala Phe Ser Glu Asp Gly			
180	185	190	
Ser Asp Pro Tyr Val Arg Met Tyr Leu Leu Pro Asp Lys Arg Arg Ser			
195	200	205	
Gly Arg Arg Lys Thr His Val Ser Lys Lys Thr Leu Asn Pro Val Phe			
210	215	220	
Asp Gln Ser Phe Asp Phe Ser Val Ser Leu Pro Glu Val Gln Arg Arg			
225	230	235	240
Thr Leu Asp Val Ala Val Lys Asn Ser Gly Gly Phe Leu Ser Lys Asp			
245	250	255	
Lys Gly Leu Leu Gly Lys Val Leu Val Ala Leu Ala Ser Glu Glu Leu			
260	265	270	
Ala Lys Gly Trp Thr Gln Trp Tyr Asp Leu Thr Glu Asp Gly Thr Arg			
275	280	285	
Pro Gln Ala Met Thr			
290			

## (2) INFORMATION FOR SEQ ID NO:23:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 206 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Met	Glu	Arg	Arg	His	Pro	Val	Cys	Ser	Gly	Thr	Cys	Gln	Pro	Thr	Gln
1				5					10					15	
Phe	Arg	Cys	Ser	Asn	Gly	Cys	Cys	Ile	Asp	Ser	Phe	Leu	Glu	Cys	Asp
			20					25					30		
Asp	Thr	Pro	Asn	Cys	Pro	Asp	Ala	Ser	Asp	Glu	Ala	Ala	Cys	Glu	Lys
		35					40					45			
Tyr	Thr	Ser	Gly	Phe	Asp	Glu	Leu	Gln	Arg	Ile	His	Phe	Pro	Ser	Asp
	50					55					60				
Lys	Gly	His	Cys	Val	Asp	Leu	Pro	Asp	Thr	Gly	Leu	Cys	Lys	Glu	Ser
65				70					75					80	
Ile	Pro	Arg	Trp	Tyr	Tyr	Asn	Pro	Phe	Ser	Glu	His	Cys	Ala	Arg	Phe
			85						90					95	
Thr	Tyr	Gly	Gly	Cys	Tyr	Gly	Asn	Lys	Asn	Asn	Phe	Glu	Glu	Glu	Gln
		100						105					110		
Gln	Cys	Leu	Glu	Ser	Cys	Arg	Gly	Ile	Ser	Lys	Lys	Asp	Val	Phe	Gly
	115						120					125			
Leu	Arg	Arg	Glu	Ile	Pro	Ile	Pro	Ser	Thr	Gly	Ser	Val	Glu	Met	Ala
	130					135					140				
Val	Ala	Val	Phe	Leu	Val	Ile	Cys	Ile	Val	Val	Val	Val	Ala	Ile	Leu
145				150					155					160	
Gly	Tyr	Cys	Phe	Phe	Lys	Asn	Gln	Arg	Lys	Asp	Phe	His	Gly	His	His
			165						170				175		
His	His	Pro	Pro	Pro	Thr	Pro	Ala	Ser	Ser	Thr	Val	Ser	Thr	Thr	Glu
		180						185					190		
Asp	Thr	Glu	His	Leu	Val	Tyr	Asn	His	Thr	Thr	Arg	Pro	Leu		
	195						200					205			

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 220 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```

Met Ala Gly Leu Ser Arg Gly Ser Ala Arg Ala Leu Leu Ala Ala Leu
 1           5           10           15
Leu Ala Ser Thr Leu Leu Ala Leu Leu Val Ser Pro Ala Arg Gly Arg
      20           25           30
Gly Gly Arg Asp His Gly Asp Trp Asp Glu Ala Ser Arg Leu Pro Pro
      35           40           45
Leu Pro Pro Arg Glu Asp Ala Ala Arg Val Ala Arg Phe Val Thr His
      50           55           60
Val Ser Asp Trp Gly Ala Leu Ala Thr Ile Ser Thr Leu Glu Ala Val
      65           70           75           80
Arg Gly Arg Pro Phe Ala Asp Val Leu Ser Leu Ser Asp Gly Pro Pro
      85           90           95
Gly Ala Gly Ser Gly Val Pro Tyr Phe Tyr Leu Ser Pro Leu Gln Leu
      100          105          110
Ser Val Ser Asn Leu Gln Glu Asn Pro Tyr Ala Thr Leu Thr Met Thr
      115          120          125
Leu Ala Gln Thr Asn Phe Cys Lys Lys His Gly Phe Asp Pro Gln Ser
      130          135          140
Pro Leu Cys Val His Ile Met Leu Ser Gly Thr Val Thr Lys Val Asn
      145          150          155          160
Glu Thr Glu Met Asp Ile Ala Lys His Ser Leu Phe Ile Arg His Pro
      165          170          175
Glu Met Lys Thr Trp Pro Ser Ser His Asn Trp Phe Phe Ala Lys Leu
      180          185          190
Asn Ile Thr Asn Ile Trp Val Leu Asp Tyr Phe Gly Gly Pro Lys Ile
      195          200          205
Val Thr Pro Glu Glu Tyr Tyr Asn Val Thr Val Gln

```

210

215

220

## (2) INFORMATION FOR SEQ ID NO:25:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 197 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```

Met Asp His His Cys Pro Trp Leu Asn Asn Cys Val Gly His Tyr Asn
 1             5             10             15
His Arg Tyr Phe Phe Ser Phe Cys Phe Phe Met Thr Leu Gly Cys Val
      20             25             30
Tyr Cys Ser Tyr Gly Ser Trp Asp Leu Phe Arg Glu Ala Tyr Ala Ala
      35             40             45
Ile Glu Lys Met Lys Gln Leu Asp Lys Asn Lys Leu Gln Ala Val Ala
      50             55             60
Asn Gln Thr Tyr His Gln Thr Pro Pro Pro Thr Phe Ser Phe Arg Glu
      65             70             75             80
Arg Met Thr His Lys Ser Leu Val Tyr Leu Trp Phe Leu Cys Ser Ser
      85             90             95
Val Ala Leu Ala Leu Gly Ala Leu Thr Val Trp His Ala Val Leu Ile
      100            105            110
Ser Arg Gly Glu Thr Ser Ile Glu Arg His Ile Asn Lys Lys Glu Arg
      115            120            125
Arg Arg Leu Gln Ala Lys Gly Arg Val Phe Arg Asn Pro Tyr Asn Tyr
      130            135            140
Gly Cys Leu Asp Asn Trp Lys Val Phe Leu Gly Val Asp Thr Gly Arg
      145            150            155            160
His Trp Leu Thr Arg Val Leu Leu Pro Ser Thr His Leu Pro His Gly
      165            170            175

```



Asn Gly Met Ser Trp Glu Pro Pro Pro Trp Val Thr Ala His Ser Ala  
 180 185 190  
 Ser Val Met Ala Val  
 195

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 451 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met Ala Pro Leu Gly Met Leu Leu Gly Leu Leu Met Ala Ala Cys Phe  
 1 5 10 15  
 Thr Phe Cys Leu Ser His Gln Asn Leu Lys Glu Phe Ala Leu Thr Asn  
 20 25 30  
 Pro Glu Lys Ser Ser Thr Lys Glu Thr Glu Arg Lys Glu Thr Lys Ala  
 35 40 45  
 Glu Glu Glu Leu Asp Ala Glu Val Leu Glu Val Phe His Pro Thr His  
 50 55 60  
 Glu Trp Gln Ala Leu Gln Pro Gly Gln Ala Val Pro Ala Gly Ser His  
 65 70 75 80  
 Val Arg Leu Asn Leu Gln Thr Gly Glu Arg Glu Ala Lys Leu Gln Tyr  
 85 90 95  
 Glu Asp Lys Phe Arg Asn Asn Leu Lys Gly Lys Arg Leu Asp Ile Asn  
 100 105 110  
 Thr Asn Thr Tyr Thr Ser Gln Asp Leu Lys Ser Ala Leu Ala Lys Phe  
 115 120 125  
 Lys Glu Gly Ala Glu Met Glu Ser Ser Lys Glu Asp Lys Ala Arg Gln  
 130 135 140  
 Ala Glu Val Lys Arg Leu Phe Arg Pro Ile Glu Glu Leu Lys Lys Asp

145	150	155	160
Phe Asp Glu Leu Asn Val Val Ile Glu Thr Asp Met Gln Ile Met Val			
165	170	175	
Arg Leu Ile Asn Lys Phe Asn Ser Ser Ser Ser Ser Leu Glu Glu Lys			
180	185	190	
Ile Ala Ala Leu Phe Asp Leu Glu Tyr Tyr Val His Gln Met Asp Asn			
195	200	205	
Ala Gln Asp Leu Leu Ser Phe Gly Gly Leu Gln Val Val Ile Asn Gly			
210	215	220	
Leu Asn Ser Thr Glu Pro Leu Val Lys Glu Tyr Ala Ala Phe Val Leu			
225	230	235	240
Gly Ala Ala Phe Ser Ser Asn Pro Lys Val Gln Val Glu Ala Ile Glu			
245	250	255	
Gly Gly Ala Leu Gln Lys Leu Leu Val Ile Leu Ala Thr Glu Gln Pro			
260	265	270	
Leu Thr Ala Lys Lys Lys Val Leu Phe Ala Leu Cys Ser Leu Leu Arg			
275	280	285	
His Phe Pro Tyr Ala Gln Arg Gln Phe Leu Lys Leu Gly Gly Leu Gln			
290	295	300	
Val Leu Arg Thr Leu Val Gln Glu Lys Gly Thr Glu Val Leu Ala Val			
305	310	315	320
Arg Val Val Thr Leu Leu Tyr Asp Leu Val Thr Glu Lys Met Phe Ala			
325	330	335	
Glu Glu Glu Ala Glu Leu Thr Gln Glu Met Ser Pro Glu Lys Leu Gln			
340	345	350	
Gln Tyr Arg Gln Val His Leu Leu Pro Gly Leu Trp Glu Gln Gly Trp			
355	360	365	
Cys Glu Ile Thr Ala His Leu Leu Ala Leu Pro Glu His Asp Ala Arg			
370	375	380	
Glu Lys Val Leu Gln Thr Leu Gly Val Leu Leu Thr Thr Cys Arg Asp			
385	390	395	400
Arg Tyr Arg Gln Asp Pro Gln Leu Gly Arg Thr Leu Ala Ser Leu Gln			
405	410	415	
Ala Glu Tyr Gln Val Leu Ala Ser Leu Glu Leu Gln Asp Gly Glu Asp			
420	425	430	
Glu Gly Tyr Phe Gln Glu Leu Leu Gly Ser Val Asn Ser Leu Leu Lys			

435                                      440                                      445  
 Glu Leu Arg  
 450

## (2) INFORMATION FOR SEQ ID NO:27:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 254 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Met Trp Gln Ala Gly Lys Arg Gln Ala Ser Arg Ala Phe Ser Leu Tyr  
 1                                      5                                      10                                      15  
 Ala Asn Ile Asp Ile Leu Arg Pro Tyr Phe Asp Val Glu Pro Ala Gln  
                                     20                                      25                                      30  
 Val Arg Ser Arg Leu Leu Glu Ser Met Ile Pro Ile Lys Met Val Asn  
                                     35                                      40                                      45  
 Phe Pro Gln Lys Ile Ala Gly Glu Leu Tyr Gly Pro Leu Met Leu Val  
                                     50                                      55                                      60  
 Phe Thr Leu Val Ala Ile Leu Leu His Gly Met Lys Thr Ser Asp Thr  
 65                                      70                                      75                                      80  
 Ile Ile Arg Glu Gly Thr Leu Met Gly Thr Ala Ile Gly Thr Cys Phe  
                                     85                                      90                                      95  
 Gly Tyr Trp Leu Gly Val Ser Ser Phe Ile Tyr Phe Leu Ala Tyr Leu  
                                     100                                      105                                      110  
 Cys Asn Ala Gln Ile Thr Met Leu Gln Met Leu Ala Leu Leu Gly Tyr  
                                     115                                      120                                      125  
 Gly Leu Phe Gly His Cys Ile Val Leu Phe Ile Thr Tyr Asn Ile His  
                                     130                                      135                                      140  
 Leu His Ala Leu Phe Tyr Leu Phe Trp Leu Leu Val Gly Gly Leu Ser  
 145                                      150                                      155                                      160

Thr Leu Arg Met Val Ala Val Leu Val Ser Arg Thr Val Gly Pro Thr  
                     165                    170                    175  
 Gln Arg Leu Leu Leu Cys Gly Thr Leu Ala Ala Leu His Met Leu Phe  
                     180                    185                    190  
 Leu Leu Tyr Leu His Phe Ala Tyr His Lys Val Val Glu Gly Ile Leu  
                     195                    200                    205  
 Asp Thr Leu Glu Gly Pro Asn Ile Pro Pro Ile Gln Arg Val Pro Arg  
                     210                    215                    220  
 Asp Ile Pro Ala Met Leu Pro Ala Ala Arg Leu Pro Thr Thr Val Leu  
                     225                    230                    235                    240  
 Asn Ala Thr Ala Lys Ala Val Ala Val Thr Leu Gln Ser His  
                     245                    250

## (2) INFORMATION FOR SEQ ID NO:28:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 221 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Gly Ser Glu Asn Glu Ala Leu Asp Leu Ser Met Lys Ser Val Pro  
   1                    5                    10                    15  
 Trp Leu Lys Ala Gly Glu Val Ser Pro Pro Ile Phe Gln Glu Asp Ala  
                     20                    25                    30  
 Ala Leu Asp Leu Ser Val Ala Ala His Arg Lys Ser Glu Pro Pro Pro  
                     35                    40                    45  
 Glu Thr Leu Tyr Asp Ser Gly Ala Ser Val Asp Ser Ser Gly His Thr  
                     50                    55                    60  
 Val Met Glu Lys Leu Pro Ser Gly Met Glu Ile Ser Phe Ala Pro Ala  
                     65                    70                    75                    80  
 Thr Ser His Glu Ala Pro Ala Met Met Asp Ser His Ile Ser Ser Ser

85	90	95
Asp Ala Ala Thr Glu Met Leu Ser Gln Pro Asn His Pro Ser Gly Glu		
100	105	110
Val Lys Ala Glu Asn Asn Ile Glu Met Val Gly Glu Ser Gln Ala Ala		
115	120	125
Lys Val Ile Val Ser Val Glu Asp Ala Val Pro Thr Ile Phe Cys Gly		
130	135	140
Lys Ile Lys Gly Leu Ser Gly Val Ser Thr Lys Asn Phe Ser Phe Lys		
145	150	155
Arg Glu Asp Ser Val Leu Gln Gly Tyr Asp Ile Asn Ser Gln Gly Glu		
165	170	175
Glu Ser Met Gly Asn Ala Glu Pro Leu Arg Lys Pro Ile Lys Asn Arg		
180	185	190
Ser Ile Lys Leu Lys Lys Val Asn Ser Gln Glu Val His Met Leu Pro		
195	200	205
Ile Lys Lys Gln Arg Leu Ala Thr Phe Phe Pro Arg Lys		
210	215	220

## (2) INFORMATION FOR SEQ ID NO:29:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 266 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Met Val Lys Val Thr Phe Asn Ser Ala Leu Ala Gln Lys Glu Ala Lys		
1	5	10
Lys Asp Glu Pro Lys Ser Gly Glu Glu Ala Leu Ile Ile Pro Pro Asp		
20	25	30
Ala Val Ala Val Asp Cys Lys Asp Pro Asp Asp Val Val Pro Val Gly		
35	40	45

Gln Arg Arg Ala Trp Cys Trp Cys Met Cys Phe Gly Leu Ala Phe Met		
50	55	60
Leu Ala Gly Val Ile Leu Gly Gly Ala Tyr Leu Tyr Lys Tyr Phe Ala		
65	70	75 80
Leu Gln Pro Asp Asp Val Tyr Tyr Cys Gly Ile Lys Tyr Ile Lys Asp		
85	90	95
Asp Val Ile Leu Asn Glu Pro Ser Ala Asp Ala Pro Ala Ala Leu Tyr		
100	105	110
Gln Thr Ile Glu Glu Asn Ile Lys Ile Phe Glu Glu Glu Glu Val Glu		
115	120	125
Phe Ile Ser Val Pro Val Pro Glu Phe Ala Asp Ser Asp Pro Ala Asn		
130	135	140
Ile Val His Asp Phe Asn Lys Lys Leu Thr Ala Tyr Leu Asp Leu Asn		
145	150	155 160
Leu Asp Lys Cys Tyr Val Ile Pro Leu Asn Thr Ser Ile Val Met Pro		
165	170	175
Pro Arg Asn Leu Leu Glu Leu Leu Ile Asn Ile Lys Ala Gly Thr Tyr		
180	185	190
Leu Pro Gln Ser Tyr Leu Ile His Glu His Met Val Ile Thr Asp Arg		
195	200	205
Ile Glu Asn Ile Asp His Leu Gly Phe Phe Ile Tyr Arg Leu Cys His		
210	215	220
Asp Lys Glu Thr Tyr Lys Leu Gln Arg Arg Glu Thr Ile Lys Gly Ile		
225	230	235 240
Gln Lys Arg Glu Ala Ser Asn Cys Phe Ala Ile Arg His Phe Glu Asn		
245	250	255
Lys Phe Ala Val Glu Thr Leu Ile Cys Ser		
260	265	

## (2) INFORMATION FOR SEQ ID NO:30:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 251 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```

Met Pro Thr Gly Asp Phe Asp Ser Lys Pro Ser Trp Ala Asp Gln Val
 1           5           10           15
Glu Glu Glu Gly Glu Asp Asp Lys Cys Val Thr Ser Glu Leu Leu Lys
          20           25           30
Gly Ile Pro Leu Ala Thr Gly Asp Thr Ser Pro Glu Pro Glu Leu Leu
      35           40           45
Pro Gly Ala Pro Leu Pro Pro Pro Lys Glu Val Ile Asn Gly Asn Ile
      50           55           60
Lys Thr Val Thr Glu Tyr Lys Ile Asp Glu Asp Gly Lys Lys Phe Lys
65           70           75           80
Ile Val Arg Thr Phe Arg Ile Glu Thr Arg Lys Ala Ser Lys Ala Val
          85           90           95
Ala Arg Arg Lys Asn Trp Lys Lys Phe Gly Asn Ser Glu Phe Asp Pro
          100          105          110
Pro Gly Pro Asn Val Ala Thr Thr Thr Val Ser Asp Asp Val Ser Met
          115          120          125
Thr Phe Ile Thr Ser Lys Glu Asp Leu Asn Cys Gln Glu Glu Glu Asp
          130          135          140
Pro Met Asn Lys Phe Lys Gly Gln Lys Ile Val Ser Cys Arg Ile Cys
145          150          155          160
Lys Gly Asp His Trp Thr Thr Arg Cys Pro Tyr Lys Asp Thr Leu Gly
          165          170          175
Pro Met Gln Lys Glu Leu Ala Glu Gln Leu Gly Leu Ser Thr Gly Glu
          180          185          190
Lys Glu Lys Leu Pro Gly Glu Leu Glu Pro Val Gln Ala Thr Gln Asn
          195          200          205
Lys Thr Gly Lys Tyr Val Pro Pro Ser Leu Arg Asp Gly Ala Ser Arg
          210          215          220
Arg Gly Glu Ser Met Gln Pro Asn Arg Arg Ala Asp Asp Asn Ala Thr
225          230          235          240
Ile Arg Val Thr Asn Leu Arg Arg Gly His Ala
          245          250

```

## (2) INFORMATION FOR SEQ ID NO:31:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 377 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```

Met Arg Arg Leu Asn Arg Lys Lys Thr Leu Ser Leu Val Lys Glu Leu
 1             5             10             15
Asp Ala Phe Pro Lys Val Pro Glu Ser Tyr Val Glu Thr Ser Ala Ser
      20             25             30
Gly Gly Thr Val Ser Leu Ile Ala Phe Thr Thr Met Ala Leu Leu Thr
      35             40             45
Ile Met Glu Phe Ser Val Tyr Gln Asp Thr Trp Met Lys Tyr Glu Tyr
      50             55             60
Glu Val Asp Lys Asp Phe Ser Ser Lys Leu Arg Ile Asn Ile Asp Ile
      65             70             75             80
Thr Val Ala Met Lys Cys Gln Tyr Val Gly Ala Asp Val Leu Asp Leu
      85             90             95
Ala Glu Thr Met Val Ala Ser Ala Asp Gly Leu Val Tyr Glu Pro Thr
      100            105            110
Val Phe Asp Leu Ser Pro Gln Gln Lys Glu Trp Gln Arg Met Leu Gln
      115            120            125
Leu Ile Gln Ser Arg Leu Gln Glu Glu His Ser Leu Gln Asp Val Ile
      130            135            140
Phe Lys Ser Ala Phe Lys Ser Thr Ser Thr Ala Leu Pro Pro Arg Glu
      145            150            155            160
Asp Asp Ser Ser Gln Ser Pro Asn Ala Cys Arg Ile His Gly His Leu
      165            170            175
Tyr Val Asn Lys Val Ala Gly Asn Phe His Ile Thr Val Gly Lys Ala
      180            185            190

```



Ile Pro His Pro Arg Gly His Ala His Leu Ala Ala Leu Val Asn His  
 195 200 205  
 Glu Ser Tyr Asn Phe Ser His Arg Ile Asp His Leu Ser Phe Gly Glu  
 210 215 220  
 Leu Val Pro Ala Ile Ile Asn Pro Leu Asp Gly Thr Glu Lys Ile Ala  
 225 230 235 240  
 Ile Asp His Asn Gln Met Phe Gln Tyr Phe Ile Thr Val Val Pro Thr  
 245 250 255  
 Lys Leu His Thr Tyr Lys Ile Ser Ala Asp Thr His Gln Phe Ser Val  
 260 265 270  
 Thr Glu Arg Glu Arg Ile Ile Asn His Ala Ala Gly Ser His Gly Val  
 275 280 285  
 Ser Gly Ile Phe Met Lys Tyr Asp Leu Ser Ser Leu Met Val Thr Val  
 290 295 300  
 Thr Glu Glu His Met Pro Phe Trp Gln Phe Phe Val Arg Leu Cys Gly  
 305 310 315 320  
 Ile Val Gly Gly Ile Phe Ser Thr Thr Gly Met Leu His Gly Ile Gly  
 325 330 335  
 Lys Phe Ile Val Glu Ile Ile Cys Cys Arg Phe Arg Leu Gly Ser Tyr  
 340 345 350  
 Lys Pro Val Asn Ser Val Pro Phe Glu Asp Gly His Thr Asp Asn His  
 355 360 365  
 Leu Pro Leu Leu Glu Asn Asn Thr His  
 370 375

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 250 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met Gly Ser Gln His Ser Ala Ala Ala Arg Pro Ser Ser Cys Arg Arg  
 1 5 10 15  
 Lys Gln Glu Asp Asp Arg Asp Gly Leu Leu Ala Glu Arg Glu Gln Glu  
 20 25 30  
 Glu Ala Ile Ala Gln Phe Pro Tyr Val Glu Phe Thr Gly Arg Asp Ser  
 35 40 45  
 Ile Thr Cys Leu Thr Cys Gln Gly Thr Gly Tyr Ile Pro Thr Glu Gln  
 50 55 60  
 Val Asn Glu Leu Val Ala Leu Ile Pro His Ser Asp Gln Arg Leu Arg  
 65 70 75 80  
 Pro Gln Arg Thr Lys Gln Tyr Val Leu Leu Ser Ile Leu Leu Cys Leu  
 85 90 95  
 Leu Ala Ser Gly Leu Val Val Phe Phe Leu Phe Pro His Ser Val Leu  
 100 105 110  
 Val Asp Asp Asp Gly Ile Lys Val Val Lys Val Thr Phe Asn Lys Gln  
 115 120 125  
 Asp Ser Leu Val Ile Leu Thr Ile Met Ala Thr Leu Lys Ile Arg Asn  
 130 135 140  
 Ser Asn Phe Tyr Thr Val Ala Val Thr Ser Leu Ser Ser Gln Ile Gln  
 145 150 155 160  
 Tyr Met Asn Thr Val Val Ser Thr Tyr Val Thr Thr Asn Val Ser Leu  
 165 170 175  
 Ile Pro Pro Arg Ser Glu Gln Leu Val Asn Phe Thr Gly Lys Ala Glu  
 180 185 190  
 Met Gly Gly Pro Phe Ser Tyr Val Tyr Phe Phe Cys Thr Val Pro Glu  
 195 200 205  
 Ile Leu Val His Asn Ile Val Ile Phe Met Arg Thr Ser Val Lys Ile  
 210 215 220  
 Ser Tyr Ile Gly Leu Met Thr Gln Ser Ser Leu Glu Thr His His Tyr  
 225 230 235 240  
 Val Asp Cys Gly Gly Asn Ser Thr Ala Ile  
 245 250

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 374 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```

Met Val Thr Cys Phe His Val Pro Tyr Ser Ala Leu Thr Met Phe Ile
 1             5             10             15
Ser Thr Glu Gln Thr Glu Arg Asp Ser Ala Thr Ala Tyr Arg Met Thr
      20             25             30
Val Glu Val Leu Gly Thr Val Leu Gly Thr Ala Ile Gln Gly Gln Ile
      35             40             45
Val Gly Gln Ala Asp Thr Pro Cys Phe Gln Asp Leu Asn Ser Ser Thr
      50             55             60
Val Ala Ser Gln Ser Ala Asn His Thr His Gly Thr Thr Ser His Arg
      65             70             75             80
Glu Thr Gln Lys Ala Tyr Leu Leu Ala Ala Gly Val Ile Val Cys Ile
      85             90             95
Tyr Ile Ile Cys Ala Val Ile Leu Ile Leu Gly Val Arg Glu Gln Arg
      100            105            110
Glu Pro Tyr Glu Ala Gln Gln Ser Glu Pro Ile Ala Tyr Phe Arg Gly
      115            120            125
Leu Arg Leu Val Met Ser His Gly Pro Tyr Ile Lys Leu Ile Thr Gly
      130            135            140
Phe Leu Phe Thr Ser Leu Ala Phe Met Leu Val Glu Gly Asn Phe Val
      145            150            155            160
Leu Phe Cys Thr Tyr Thr Leu Gly Phe Arg Asn Glu Phe Gln Asn Leu
      165            170            175
Leu Leu Ala Ile Met Leu Ser Ala Thr Leu Thr Ile Pro Ile Trp Gln
      180            185            190
Trp Phe Leu Thr Arg Phe Gly Lys Lys Thr Ala Val Tyr Val Gly Ile
      195            200            205
Ser Ser Ala Val Pro Phe Leu Ile Leu Val Ala Leu Met Glu Ser Asn

```

(2) INFORMATION FOR SEQ ID NO:34:

(A) LENGTH: 334 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

66

Gly Gln Val Leu Ala Gly Arg Ala Arg Arg Leu Leu Leu Gln Phe Gly  
 20 25 30  
 Val Leu Phe Cys Thr Ile Leu Leu Leu Leu Trp Val Ser Val Phe Leu  
 35 40 45  
 Tyr Gly Ser Phe Tyr Tyr Ser Tyr Met Pro Thr Val Ser His Leu Ser  
 50 55 60  
 Pro Val His Phe Tyr Tyr Arg Thr Asp Cys Asp Ser Ser Thr Thr Ser  
 65 70 75 80  
 Leu Cys Ser Phe Pro Val Ala Asn Val Ser Leu Thr Lys Gly Gly Arg  
 85 90 95  
 Asp Arg Val Leu Met Tyr Gly Gln Pro Tyr Arg Val Thr Leu Glu Leu  
 100 105 110  
 Glu Leu Pro Glu Ser Pro Val Asn Gln Asp Leu Gly Met Phe Leu Val  
 115 120 125  
 Thr Ile Ser Cys Tyr Thr Arg Gly Gly Arg Ile Ile Ser Thr Ser Ser  
 130 135 140  
 Arg Ser Val Met Leu His Tyr Arg Ser Asp Leu Leu Gln Met Leu Asp  
 145 150 155 160  
 Thr Leu Val Phe Ser Ser Leu Leu Leu Phe Gly Phe Ala Glu Gln Lys  
 165 170 175  
 Gln Leu Leu Glu Val Glu Leu Tyr Ala Asp Tyr Arg Glu Asn Ser Tyr  
 180 185 190  
 Val Pro Thr Thr Gly Ala Ile Ile Glu Ile His Ser Lys Arg Ile Gln  
 195 200 205  
 Leu Tyr Gly Ala Tyr Leu Arg Ile His Ala His Phe Thr Gly Leu Arg  
 210 215 220  
 Tyr Leu Leu Tyr Asn Phe Pro Met Thr Cys Ala Phe Ile Gly Val Ala  
 225 230 235 240  
 Ser Asn Phe Thr Phe Leu Ser Val Ile Val Leu Phe Ser Tyr Met Gln  
 245 250 255  
 Trp Val Trp Gly Gly Ile Trp Pro Arg His Arg Phe Ser Leu Gln Val  
 260 265 270  
 Asn Ile Arg Lys Arg Asp Asn Ser Arg Lys Glu Val Gln Arg Arg Ile  
 275 280 285  
 Ser Ala His Gln Pro Gly Pro Glu Gly Gln Glu Glu Ser Thr Pro Gln  
 290 295 300

Ser Asp Val Thr Glu Asp Gly Glu Ser Pro Glu Asp Pro Ser Gly Thr  
 305                                      310                                      315                                      320  
 Glu Val Ser Cys Pro Arg Arg Arg Asn Gln Ile Ser Ser Pro  
    325                                      330

## (2) INFORMATION FOR SEQ ID NO:35:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 276 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Met Thr His Pro Gly Thr Gly Asp Ile Ile Ala Val Met Ile Thr Glu  
 1                                      5                                      10                                      15  
 Leu Arg Gly Lys Asp Ile Leu Ser Tyr Leu Glu Lys Asn Ile Ser Val  
    20                                      25                                      30  
 Gln Met Thr Ile Ala Val Gly Thr Arg Met Pro Pro Lys Asn Phe Ser  
    35                                      40                                      45  
 Arg Gly Ser Leu Val Phe Val Ser Ile Ser Phe Ile Val Leu Met Ile  
    50                                      55                                      60  
 Ile Ser Ser Ala Trp Leu Ile Phe Tyr Phe Ile Gln Lys Ile Arg Tyr  
 65                                      70                                      75                                      80  
 Thr Asn Ala Arg Asp Arg Asn Gln Arg Arg Leu Gly Asp Ala Ala Lys  
    85                                      90                                      95  
 Lys Ala Ile Ser Lys Leu Thr Thr Arg Thr Val Lys Lys Gly Asp Lys  
    100                                      105                                      110  
 Glu Thr Asp Pro Asp Phe Asp His Cys Ala Val Cys Ile Glu Ser Tyr  
    115                                      120                                      125  
 Lys Gln Asn Asp Val Val Arg Ile Leu Pro Cys Lys His Val Phe His  
    130                                      135                                      140  
 Lys Ser Cys Val Asp Pro Trp Leu Ser Glu His Cys Thr Cys Pro Met

```

145             150             155             160
Cys Lys Leu Asn Ile Leu Lys Ala Leu Gly Ile Val Pro Asn Leu Pro
             165             170             175
Cys Thr Asp Asn Val Ala Phe Asp Met Glu Arg Leu Thr Arg Thr Gln
             180             185             190
Ala Val Asn Arg Arg Ser Ala Leu Gly Asp Leu Ala Gly Asp Asn Ser
             195             200             205
Leu Gly Leu Glu Pro Leu Arg Thr Ser Gly Ile Ser Pro Leu Pro Gln
             210             215             220
Asp Gly Glu Leu Thr Pro Arg Thr Gly Glu Ile Asn Ile Ala Val Thr
225             230             235             240
Lys Glu Trp Phe Ile Ile Ala Ser Phe Gly Leu Leu Ser Ala Leu Thr
             245             250             255
Leu Cys Tyr Met Ile Ile Arg Ala Thr Ala Ser Leu Asn Ala Asn Glu
             260             265             270
Val Glu Trp Phe
             275

```

## (2) INFORMATION FOR SEQ ID NO:36:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 210 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

```

Met Ala Asn Ser Gly Leu Gln Leu Leu Gly Phe Ser Met Ala Leu Leu
 1             5             10             15
Gly Trp Val Gly Leu Val Ala Cys Thr Ala Ile Pro Gln Trp Gln Met
             20             25             30
Ser Ser Tyr Ala Gly Asp Asn Ile Ile Thr Ala Gln Ala Met Tyr Lys
             35             40             45

```

Gly	Leu	Trp	Met	Asp	Cys	Val	Thr	Gln	Ser	Thr	Gly	Met	Met	Ser	Cys	
50									60							
Lys	Met	Tyr	Asp	Ser	Val	Leu	Ala	Leu	Ser	Ala	Ala	Leu	Gln	Ala	Thr	
65			70						80							
Arg	Ala	Leu	Met	Val	Val	Ser	Leu	Val	Leu	Gly	Phe	Leu	Ala	Met	Phe	
85				90						95						
Val	Ala	Thr	Met	Gly	Met	Lys	Cys	Thr	Arg	Cys	Gly	Gly	Asp	Asp	Lys	
100				105						110						
Val	Lys	Lys	Ala	Arg	Ile	Ala	Met	Gly	Gly	Gly	Ile	Ile	Phe	Ile	Val	
115			120						125							
Ala	Gly	Leu	Ala	Ala	Leu	Val	Ala	Cys	Ser	Trp	Tyr	Gly	His	Gln	Ile	
130			135						140							
Val	Thr	Asp	Phe	Tyr	Asn	Pro	Leu	Ile	Pro	Thr	Asn	Ile	Lys	Tyr	Glu	
145			150						155						160	
Phe	Gly	Pro	Ala	Ile	Phe	Ile	Gly	Trp	Ala	Gly	Ser	Ala	Leu	Val	Ile	
165				170						175						
Leu	Gly	Gly	Ala	Leu	Leu	Ser	Cys	Ser	Cys	Pro	Gly	Asn	Glu	Ser	Lys	
180				185						190						
Ala	Gly	Tyr	Arg	Ala	Pro	Arg	Ser	Tyr	Pro	Lys	Ser	Asn	Ser	Ser	Lys	
195			200						205							
Glu Tyr																
210																

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 476 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Met Ile Arg Pro Gln Leu Arg Thr Ala Gly Leu Gly Arg Cys Leu Leu



1	5	10	15
Pro Gly Leu Leu Leu Leu Leu Val Pro Val Leu Trp Ala Gly Ala Glu			
20	25	30	
Lys Leu His Thr Gln Pro Ser Cys Pro Ala Val Cys Gln Pro Thr Arg			
35	40	45	
Cys Pro Ala Leu Pro Thr Cys Ala Leu Gly Thr Thr Pro Val Phe Asp			
50	55	60	
Leu Cys Arg Cys Cys Arg Val Cys Pro Ala Ala Glu Arg Glu Val Cys			
65	70	75	80
Gly Gly Ala Gln Gly Gln Pro Cys Ala Pro Gly Leu Gln Cys Leu Gln			
85	90	95	
Pro Leu Arg Pro Gly Phe Pro Ser Thr Cys Gly Cys Pro Thr Leu Gly			
100	105	110	
Gly Ala Val Cys Gly Ser Asp Arg Arg Thr Tyr Pro Ser Met Cys Ala			
115	120	125	
Leu Arg Ala Glu Asn Arg Ala Ala Arg Arg Leu Gly Lys Val Pro Ala			
130	135	140	
Val Pro Val Gln Trp Gly Asn Cys Gly Asp Thr Gly Thr Arg Ser Ala			
145	150	155	160
Gly Pro Leu Arg Arg Asn Tyr Asn Phe Ile Ala Ala Val Val Glu Lys			
165	170	175	
Val Ala Pro Ser Val Val His Val Gln Leu Trp Gly Arg Leu Leu His			
180	185	190	
Gly Ser Arg Leu Val Pro Val Tyr Ser Gly Ser Gly Phe Ile Val Ser			
195	200	205	
Glu Asp Gly Leu Ile Ile Thr Asn Ala His Val Val Arg Asn Gln Gln			
210	215	220	
Trp Ile Glu Val Val Leu Gln Asn Gly Ala Arg Tyr Glu Ala Val Val			
225	230	235	240
Lys Asp Ile Asp Leu Lys Leu Asp Leu Ala Val Ile Lys Ile Glu Ser			
245	250	255	
Asn Ala Glu Leu Pro Val Leu Met Leu Gly Arg Ser Ser Asp Leu Arg			
260	265	270	
Ala Gly Glu Phe Val Val Ala Leu Gly Ser Pro Phe Ser Leu Gln Asn			
275	280	285	
Thr Ala Thr Ala Gly Ile Val Ser Thr Lys Gln Arg Gly Gly Lys Glu			

290	295	300
Leu Gly Met Lys Asp Ser Asp Met Asp Tyr Val Gln Ile Asp Ala Thr		
305	310	315
Ile Asn Tyr Gly Asn Ser Gly Gly Pro Leu Val Asn Leu Asp Gly Asp		320
	325	330
Val Ile Gly Val Asn Ser Leu Arg Val Thr Asp Gly Ile Ser Phe Ala		335
	340	345
Ile Pro Ser Asp Arg Val Arg Gln Phe Leu Ala Glu Tyr His Glu His		350
	355	360
Gln Met Lys Gly Lys Ala Phe Ser Asn Lys Lys Tyr Leu Gly Leu Gln		365
	370	375
Met Leu Ser Leu Thr Val Pro Leu Ser Glu Glu Leu Lys Met His Tyr		380
	385	390
Pro Asp Phe Pro Asp Val Ser Ser Gly Val Tyr Val Cys Lys Val Val		395
	405	410
Glu Gly Thr Ala Ala Gln Ser Ser Gly Leu Arg Asp His Asp Val Ile		415
	420	425
Val Asn Ile Asn Gly Lys Pro Ile Thr Thr Thr Thr Asp Val Val Lys		430
	435	440
Ala Leu Asp Ser Asp Ser Leu Ser Met Ala Val Leu Arg Gly Lys Asp		445
	450	455
Asn Leu Leu Leu Thr Val Ile Pro Glu Thr Ile Asn		460
	465	470
		475

## (2) INFORMATION FOR SEQ ID NO:38:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 266 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Met Val Lys Val Thr Phe Asn Ser Ala Leu Ala Gln Lys Glu Ala Lys  
 1 5 10 15  
 Lys Asp Glu Pro Glu Ser Gly Glu Glu Ala Leu Ile Ile Pro Pro Asp  
 20 25 30  
 Ala Val Ala Val Asp Cys Lys Asp Pro Asp Asp Val Val Pro Val Gly  
 35 40 45  
 Gln Arg Arg Ala Trp Cys Trp Cys Met Cys Phe Gly Leu Ala Phe Met  
 50 55 60  
 Leu Ala Gly Val Ile Leu Gly Gly Ala Tyr Leu Tyr Lys Tyr Phe Ala  
 65 70 75 80  
 Leu Gln Pro Asp Asp Val Tyr Tyr Cys Gly Ile Lys Tyr Ile Lys Asp  
 85 90 95  
 Asp Val Ile Leu Asn Glu Pro Ser Ala Asp Ala Pro Ala Ala Leu Tyr  
 100 105 110  
 Gln Thr Ile Glu Glu Asn Ile Lys Ile Phe Glu Glu Glu Glu Val Glu  
 115 120 125  
 Phe Ile Ser Val Pro Val Pro Glu Phe Ala Asp Ser Asp Pro Ala Asn  
 130 135 140  
 Ile Val His Asp Phe Asn Lys Lys Leu Thr Ala Tyr Leu Asp Leu Asn  
 145 150 155 160  
 Leu Asp Lys Cys Tyr Val Ile Pro Leu Asn Thr Ser Ile Val Met Pro  
 165 170 175  
 Pro Arg Asn Leu Leu Glu Leu Leu Ile Asn Ile Lys Ala Gly Thr Tyr  
 180 185 190  
 Leu Pro Gln Ser Tyr Leu Ile His Glu His Met Val Ile Thr Asp Arg  
 195 200 205  
 Ile Glu Asn Ile Asp His Leu Gly Phe Phe Ile Tyr Arg Leu Cys His  
 210 215 220  
 Asp Lys Glu Thr Tyr Lys Leu Gln Arg Arg Glu Thr Ile Lys Gly Ile  
 225 230 235 240  
 Gln Lys Arg Glu Ala Ser Asn Cys Phe Ala Ile Arg His Phe Glu Asn  
 245 250 255  
 Lys Phe Ala Val Glu Thr Leu Ile Cys Ser  
 260 265

**We Claim:**

1. An isolated and purified human protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

2. An isolated and purified human protein having an amino acid sequence which is at least 85% identical to an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

3. An isolated and purified human polypeptide comprising at least 6 contiguous amino acids of an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

4. A fusion protein comprising a first protein segment and a second protein segment fused together by means of a peptide bond, wherein the first protein segment consists of at least 6 contiguous amino acids selected from the group consisting of the amino acid sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38.

5. A preparation of antibodies which specifically bind to the human protein of claim 1.

6. An isolated and purified subgenomic polynucleotide having a nucleotide sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19.

7. An isolated gene corresponding to a cDNA sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19.

8. A DNA construct for expressing all or a portion of a human protein having an amino acid sequence selected from the group consisting of the amino acid

sequences shown in SEQ ID Nos:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38, comprising:

a promoter; and

a polynucleotide segment encoding at least 6 contiguous amino acids of the human protein, wherein the polynucleotide segment is located downstream from the promoter, wherein transcription of the polynucleotide segment initiates at or 3' to the promoter.

9. A host cell comprising a DNA construct comprising:

a promoter; and

a polynucleotide segment encoding at least 6 contiguous amino acids of a human protein having an amino acid sequence selected from the group consisting of the amino acid sequences shown in SEQ ID NOs:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38, wherein the polynucleotide segment is located downstream from the promoter and wherein transcription of the polynucleotide segment initiates at or 3' to the promoter.

10. A homologously recombinant cell having incorporated therein a new transcription initiation unit, wherein the new transcription initiation unit comprises in 5' to 3' order:

(a) an exogenous regulatory sequence;

(b) an exogenous exon; and

(c) a splice donor site,

wherein the transcription initiation unit is located upstream to a coding sequence of a gene, wherein the gene comprises a nucleotide sequence selected from the group consisting of the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19 and wherein the exogenous regulatory sequence controls transcription of the coding sequence of the gene.

11. A method of producing a human protein, comprising the steps of:

growing a culture of a cell comprising a DNA construct comprising

(1) a promoter and (2) a polynucleotide segment encoding at least 6 contiguous amino acids of a human protein having an amino acid sequence selected from the

group consisting of the amino acid sequences shown in SEQ ID NOs:20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38, wherein the polynucleotide segment is located downstream from the promoter and wherein transcription of the polynucleotide segment initiates at or 3' to the promoter; and  
5                   purifying the protein from the culture.

12.   A method of producing a human protein, comprising the steps of:  
growing a culture of a homologously recombinant cell having  
incorporated therein a new transcription initiation unit, wherein the new  
transcription initiation unit comprises in 5' to 3' order:

- 10                   (a) an exogenous regulatory sequence;  
                     (b) an exogenous exon; and  
                     (c) a splice donor site,

wherein the transcription initiation unit is located upstream to a coding sequence of  
a gene, wherein the gene comprises a nucleotide sequence selected from the group  
15                   consisting of the nucleotide sequences shown in SEQ ID NOs:1, 2, 3, 4, 5, 6, 7, 8,  
9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19 and wherein the exogenous regulatory  
sequence controls transcription of the coding sequence of the gene; and  
                     purifying the protein from the culture.

13.   A method of identifying a secreted polypeptide which is modified by  
20                   rough microsomes, comprising the steps of:  
transcribing *in vitro* a population of cDNA molecules whereby a  
population of cRNA molecules is formed;  
translating a first portion of the population of cRNA molecules *in*  
*vitro* in the absence of rough microsomes whereby a first population of polypeptides  
25                   is formed;

translating a second portion of the population of cRNA molecules *in vitro* in  
the presence of rough microsomes whereby a second population of polypeptides is  
formed;

30                   comparing the first population of polypeptides with the second  
population of polypeptides; and

detecting polypeptide members of the second population which have been modified by the rough microsomes.

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C12N 15/12, 15/62, 15/85, 5/10, 1/21,</b> <b>C07K 14/47, 16/18</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 98/25959</b> <b>(43) International Publication Date:</b> 18 June 1998 (18.06.98)
<b>(21) International Application Number:</b> PCT/US97/22787 <b>(22) International Filing Date:</b> 11 December 1997 (11.12.97) <b>(30) Priority Data:</b> 60/032,757 11 December 1996 (11.12.96) US <b>(71) Applicant:</b> CHIRON CORPORATION [US/US]; 4560 Horton Street, Emeryville, CA 94608 (US). <b>(72) Inventors:</b> ESCOBEDO, Jaime; 1470 Livorna Road, Alamo, CA 94507 (US). HU, Quianjin; Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608 (US). GARCIA, Pablo; 882 Chenery Street, San Francisco, CA 94131 (US). WILLIAMS, Lewis, T.; 3 Miraflores Lane, Tibouron, CA 94920 (US). KOTHAKOTA, Srinivas; Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608 (US). <b>(74) Agents:</b> POTTER, Jane, E., R.; Chiron Corporation, Intellectual Property - R440, P.O. Box 8097, Emeryville, CA 94662-8097 (US) et al.	<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <b>(88) Date of publication of the international search report:</b> 8 October 1998 (08.10.98)	
<b>(54) Title:</b> SECRETED HUMAN PROTEINS  <b>(57) Abstract</b>  Secreted proteins can be identified using a method which exploits the ability of microsomes to modify proteins post-translationally. Nineteen human secreted proteins and full-length cDNA sequences encoding the proteins have been identified using this method. The proteins and cDNA sequences can be used, <i>inter alia</i> , for targeting other proteins to the membrane or extracellular milieu.		



**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LJ	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 97/22787

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12N15/62 C12N15/85 C12N5/10 C12N1/21  
C07K14/47 C07K16/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 03466 A (US GOVERNMENT) 5 March 1992 see the whole document ---	1-12
A	WO 95 31560 A (TRANSKARYOTIC THERAPIES INC ;TRECO DOUGLAS A (US); HEARTLEIN MICHA) 23 November 1995 cited in the application see the whole document ---	10,12
A	TASHIRO K ET AL: "SIGNAL SEQUENCE TRAP: A CLONING STRATEGY FOR SECRETED PROTEINS AND TYPE I MEMBRANE PROTEINS" SCIENCE, vol. 261, 30 July 1993, pages 600-603, XP000673204 see the whole document ---	1-12
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

6 April 1998

Date of mailing of the international search report

28-07-1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Kania, T

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 97/22787

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JACOBS K ET AL: "A NOVEL METHOD FOR ISOLATING EUKARYOTIC CDNA CLONES ENCODING SECRETED PROTEINS" JOURNAL OF CELLULAR BIOCHEMISTRY - SUPPLEMENT, vol. 21A, 10 March 1995, page 19 XP002027246 see abstract ---	1-12
A	KLEIN R. ET AL.: "Selection of genes encoding secreted proteins and receptors" PNAS, U.S.A., vol. 93, no. 14, 9 July 1996, pages 7108-7113, XP002061411 see the whole document -----	1-12

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/ 22787

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see annex

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

claims 1-12 (partially) (Extra sheet-1)

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

1. Claims: 1-12 partially

An isolated human protein having an amino acid sequence according to SEQ ID No. 20, homologs and fragments thereof, fusion proteins therewith, antibodies thereto.  
An isolated and purified polynucleotide having the sequence according to SEQ ID No. 1, the corresponding gene, DNA constructs, host cells, and homologously recombinant cells comprising said polynucleotide.  
A method of producing said protein using said DNA sequences, constructs, or cells.

2. Claims: 1-12 partially

idem for SEQ ID 21, 2

3. Claims: 1-12 partially

idem for SEQ ID No. 22, 3

4. Claims: 1-12 partially

idem for SEQ ID No. 23, 4

5. Claims: 1-12 partially

idem for SEQ ID No. 24, 5

6. Claims: 1-12 partially

idem for SEQ ID No. 25, 6

7. Claims: 1-12 partially

idem for SEQ ID No. 26, 7

8. Claims: 1-12 partially

idem for SEQ ID No. 27, 8

9. Claims: 1-12 partially

idem for SEQ ID No. 28, 9

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

10. Claims: 1-12 partially  
idem for SEQ ID No. 29, 10
11. Claims: 1-12 partially  
idem for SEQ ID No. 30, 11
12. Claims: 1-12 partially  
idem for SEQ ID No. 31, 12
13. Claims: 1-12 partially  
idem for SEQ ID No. 32, 13
14. Claims: 1-12 partially  
idem for SEQ ID No. 33, 14
15. Claims: 1-12 partially  
idem for SEQ ID No. 34, 15
16. Claims: 1-12 partially  
idem for SEQ ID No. 35, 16
17. Claims: 1-12 partially  
idem for SEQ ID No. 36, 17
18. Claims: 1-12 partially  
idem for SEQ ID No. 37, 18
19. Claims: 1-12 partially  
idem for SEQ ID No. 38, 19

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

20. Claim : 13

A method of identifying a secreted polypeptide which is modified by rough microsomes, comprising:  
in vitro transcription of a cDNA population, translation of a first portion in the absence of rough microsomes in vitro, translation of a second portion in the presence of rough microsomes in vitro, comparison of the polypeptides of the first and second portion, and detection of members of the second portion that have been modified by the rough microsomes.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/22787

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9203466 A	05-03-1992	AU 8446891 A EP 0544743 A	17-03-1992 09-06-1993
WO 9531560 A	23-11-1995	US 5641670 A AU 2550495 A BR 9507874 A CA 2190289 A CN 1119545 A CZ 9603258 A EP 0759082 A FI 964536 A HU 76844 A JP 10500570 T NO 964802 A SK 146196 A US 5733746 A ZA 9503879 A	24-06-1997 05-12-1995 19-08-1997 23-11-1995 03-04-1996 17-12-1997 26-02-1997 09-01-1997 28-11-1997 20-01-1998 09-01-1997 04-02-1998 31-03-1998 18-01-1996